



**EHA-GBMTA-AHA Hematology
Tutorial:
New aspects in diagnostic choices
and treatment options of
hematological malignancies**

**Indolent B cell lymphomas: current
management and ongoing challenges**

Maria Gomes da Silva

18 October 2024



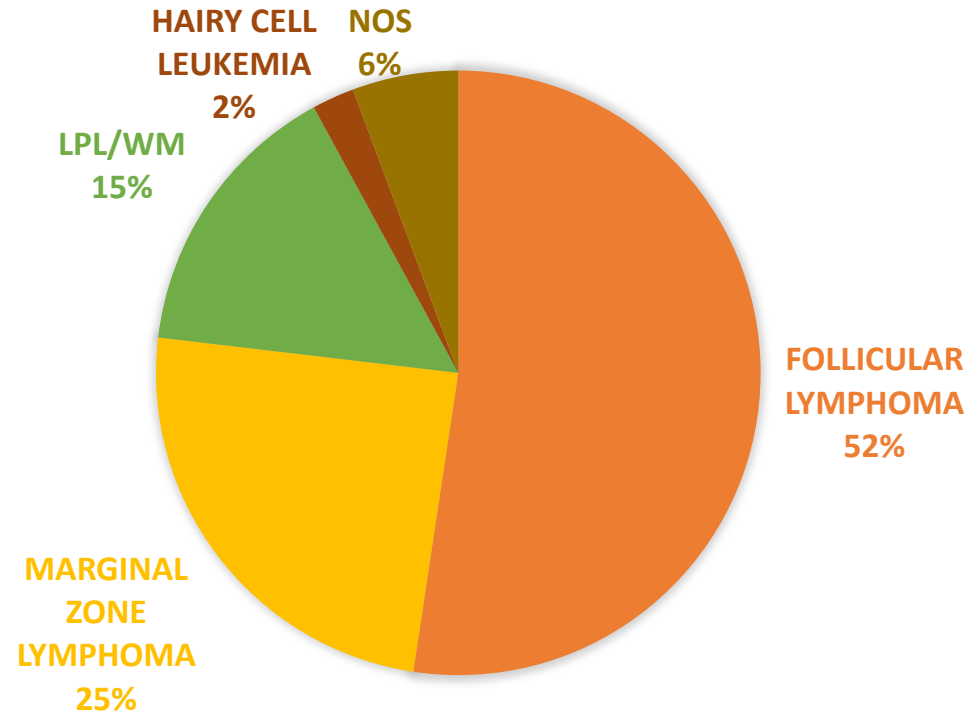
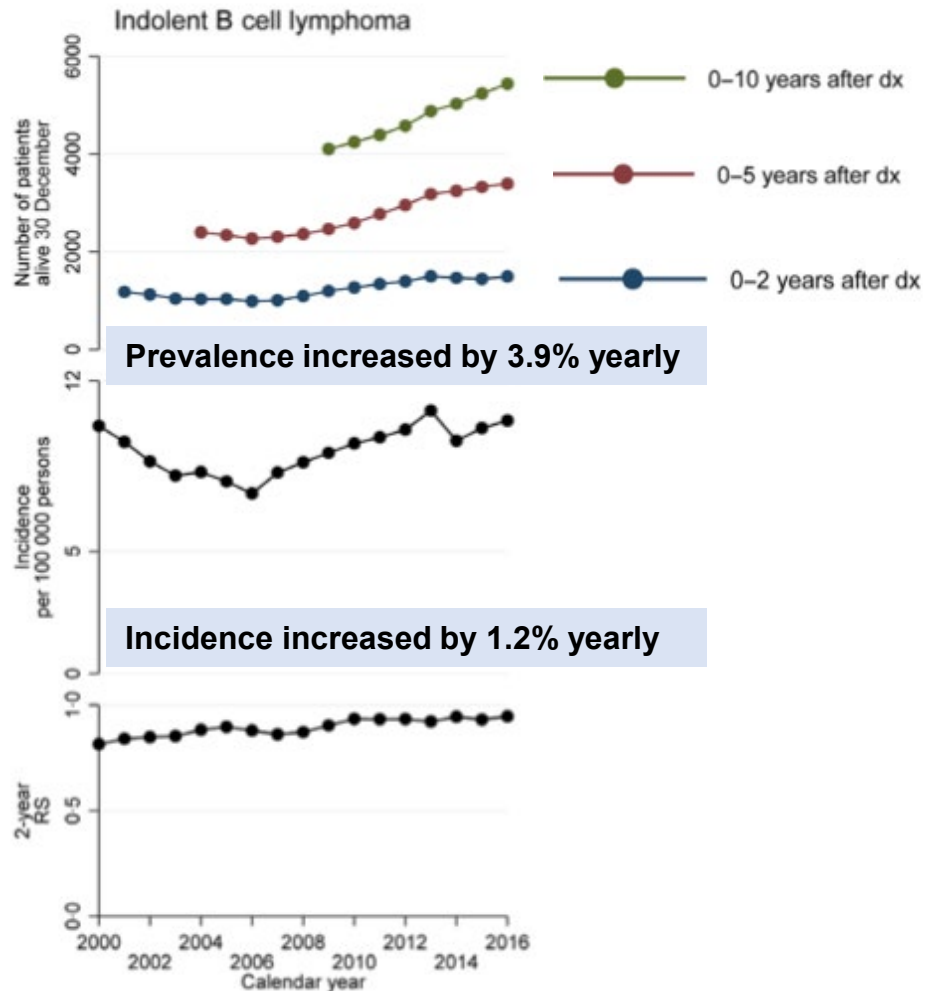
Disclosures

| | |
|---|---|
| Research Grants: | AstraZeneca |
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| Travel support | Roche, Abbvie, Janssen, Gilead |

Learning goals

- To recognize the epidemiology, clinical patterns and outcomes of the most frequent indolent lymphoma subtypes
 - Follicular lymphoma
 - Marginal zone lymphoma
 - Waldenstrom's macroglobulinemia
- To discuss prognostic factors and management according to disease and patient characteristics
- To understand the role of novel treatments in indolent lymphomas

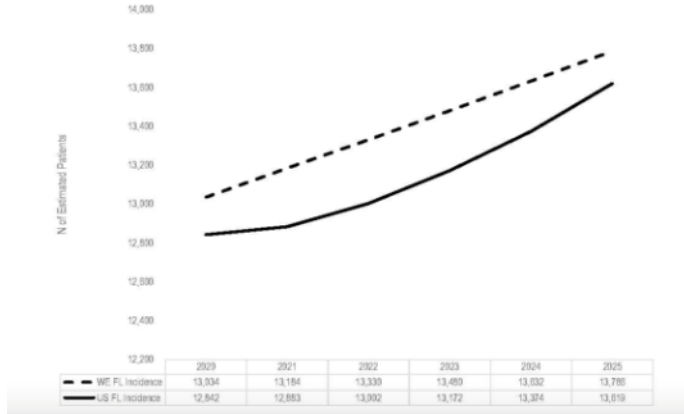
Indolent B cell lymphomas: 30 to 40% of all lymphoma cases



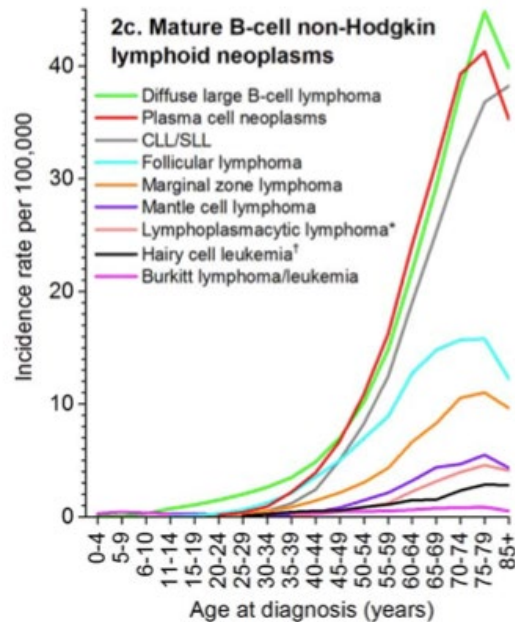
N=441 cases of iNHL diagnosed 2021-2023 at IPOL

- Indolent lymphomas: 30-40% of all NHL
- Half of iNHL are Follicular lymphomas
- Prolonged survival ⇒ increasing prevalence
- Non curable with conventional treatment

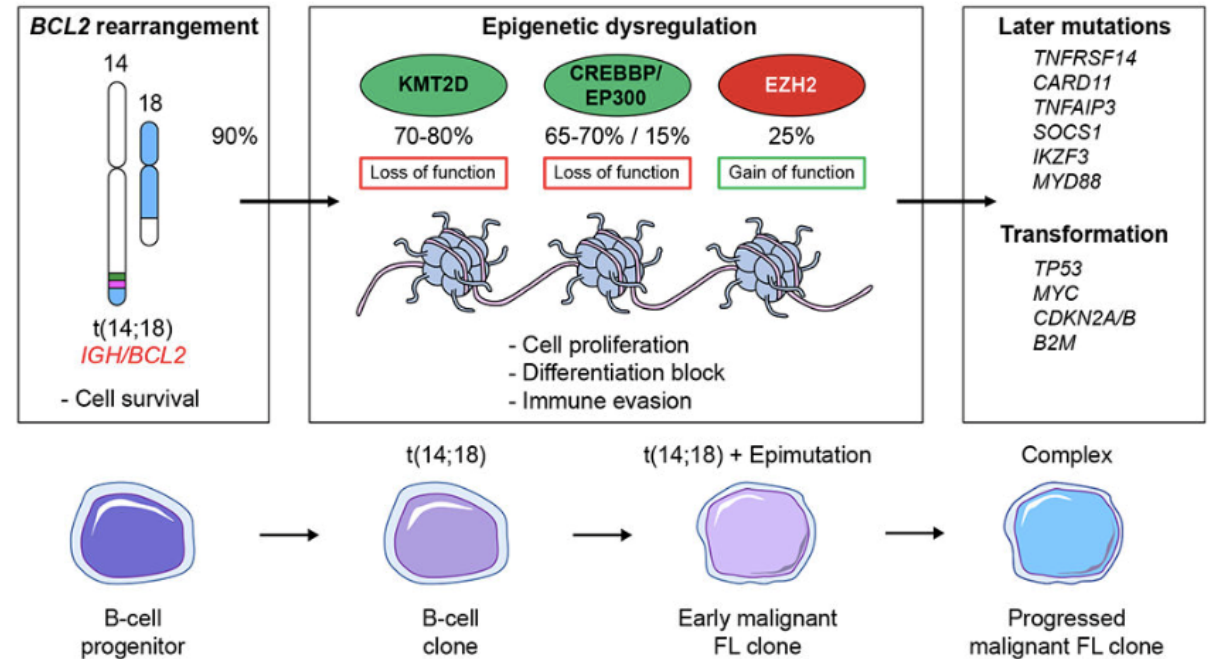
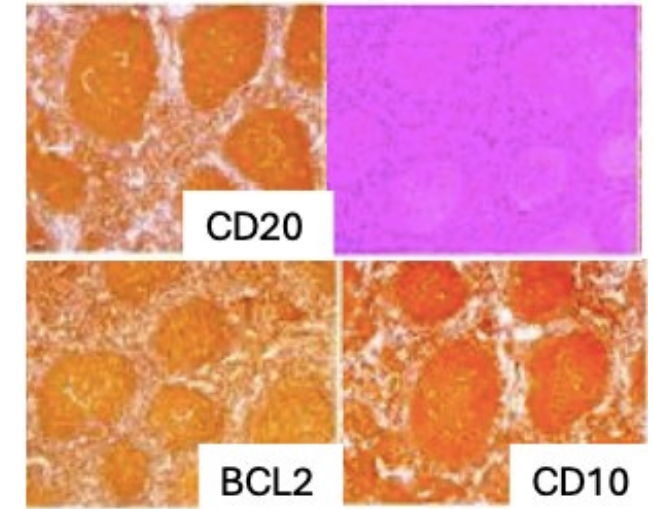
Follicular lymphoma is the most frequent iNHL



Kanas et al. Leuk Lymphoma. 2022 Jan;63(1):54-63



Median age at diagnosis **64 yo** (SEER registry)



Cahill C et al. Oncology (Williston Park). 2022 February 08; 36(2): 97–106.



Current classifications

WHO 5

Follicular lymphoma

- **Classic FL (former FL G1-G3A)**
- Predominantly diffuse
- FL with unusual cytological features
- Follicular large B cell lymphoma (former FL3B)

In situ follicular neoplasm

Duodenal type FL

Pediatric type FL

Primary cutaneous follicle center lymphoma

ICC

Follicular lymphoma (grade 1-3A; 3B)

- In situ follicular neoplasia
- Duodenal type FL

BCL2 negative, CD23 positive follicle center lymphoma

Primary cutaneous follicle center lymphoma

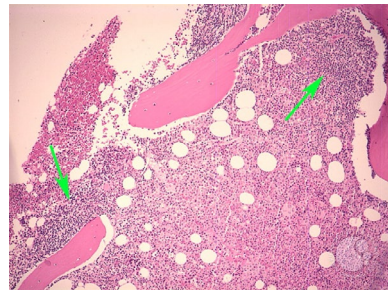
Pediatric type FL

Testicular follicular lymphoma

Large B cell lymphoma with IRF4 rearrangement

How do we stage FL and assess prognosis?

Staging



ASH databank

- Clinical examination
- CBC and chemistry panel
- Protein electrophoresis
- Viral serologies

| Risk factors | FLIPI | FLIPI2 | PRIMA PI |
|--------------|----------------|-----------------|----------------|
| | Age >60 yrs | Age>60 yrs | |
| | Hb <120g/L | Hb <120g/L | |
| | LDH >normal | BM involvement | BM involvement |
| | Stage III/IV | B2M >normal | B2M>normal |
| | >4 nodal sites | Tumor mass>6 cm | |

RISK GROUPS

Low: 5y OS 91%
 Int: 5y OS 78%
 High: 5y OS 53%

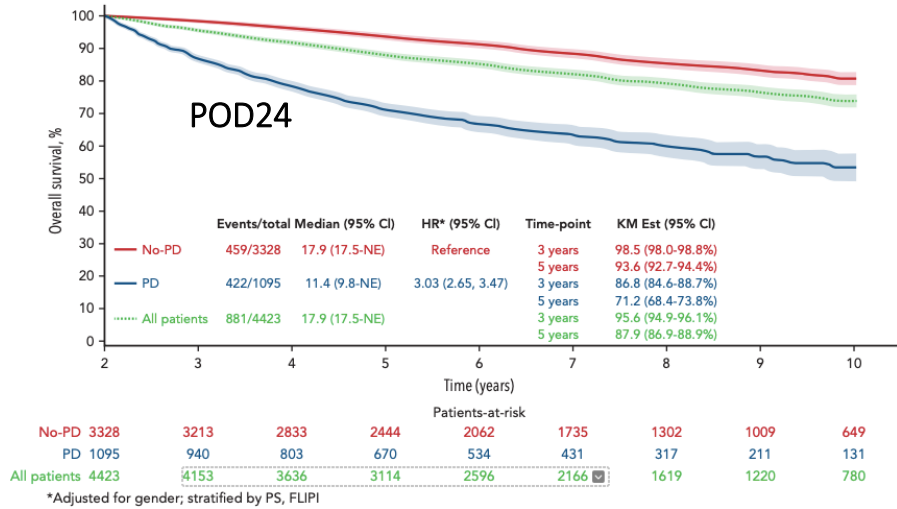
Low: 5y PFS 69%
 Int: 5y PFS 55%
 High 5y PFS 37%

Low 3y PFS 86%
 High 3yPFS 68%

Solal-Céligny P et al. *Blood*. 2004;104:1258-1265.
 Federico M et al. *J Clin Oncol*. 2009;27:4555-4562.
 Bachy E et al. *Blood*. 2018;132:49-58..

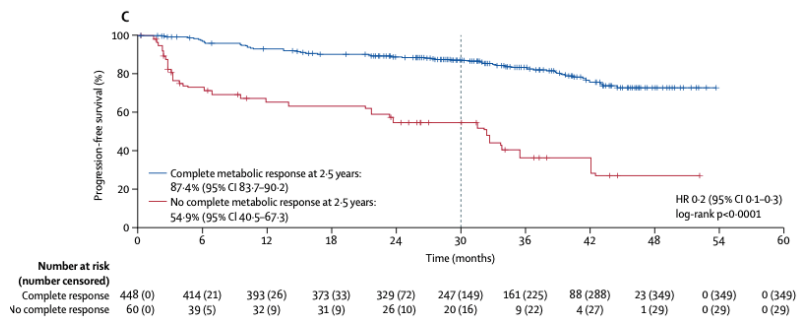
Additional factors impacting outcome

Early progression and survival in FL patients: the FLASH analysis



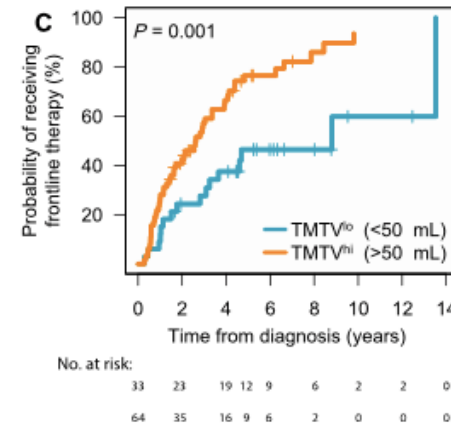
Casulo C et al, Blood 2022, 139(11): 1684

End of Induction metabolic response ⇒ PFS outcomes in GALLIUM



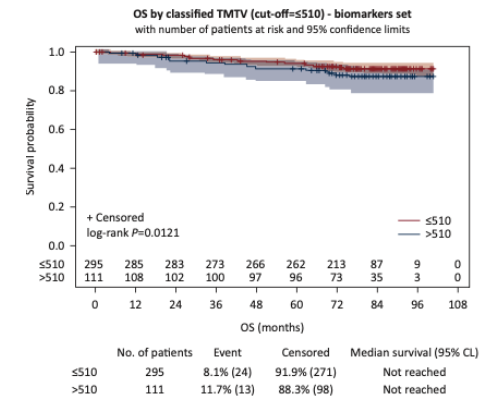
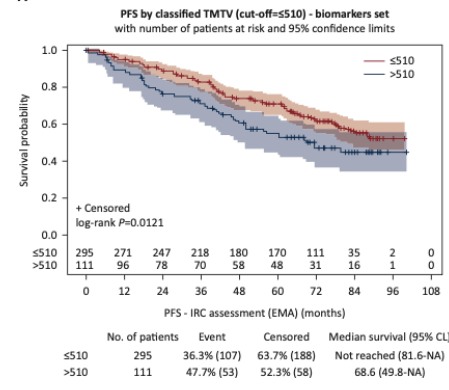
Trotman J et al, Lancet Oncol 2018, doi.org/10.1016/S1470-2045(18)30618-1

MTV in low tumor burden ⇒ probability of receiving treatment

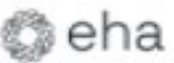


Mozas P et al, Hematol Oncol. 2024 Jan;42(1):e3235

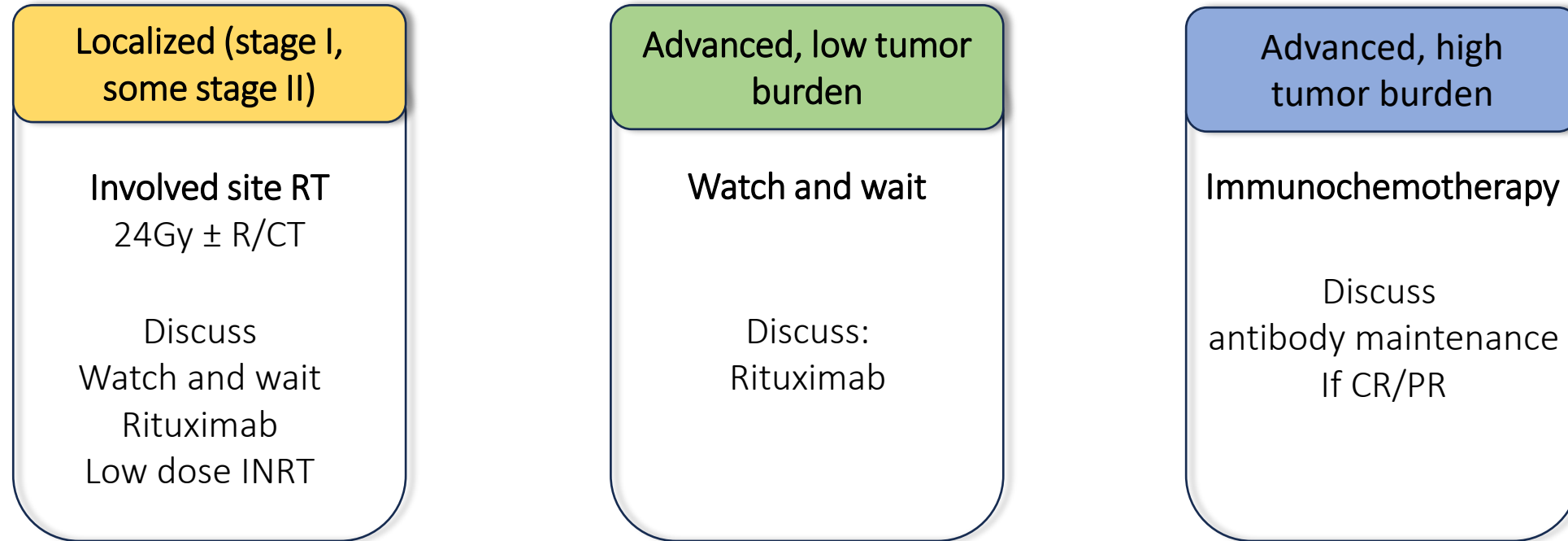
MTV in high tumor burden ⇒ outcomes



Cottreau A et al. nn Oncol. 2024 Jan;35(1):130-137



Treatment is still decided according to tumor burden, extension and symptoms



10-20%

High tumor burden
GELF criteria
BNLI criteria

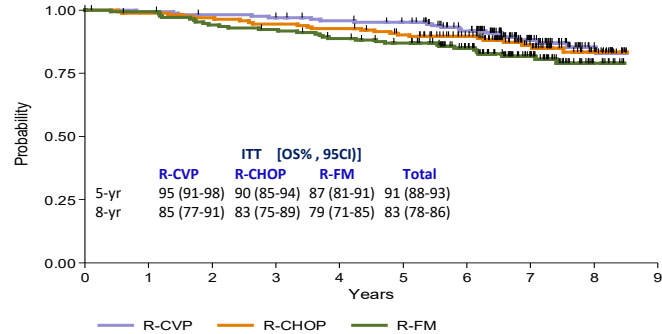
| |
|---|
| Any nodal or EN mass >7cm |
| Involvement of ≥3 nodal sites each with ≥3 cm |
| B symptoms |
| Splenomegaly below the umbilical line |
| Compressive syndrome |
| Pleural or peritoneal effusion |
| Leukemic phase |
| Cytopenias |

Dreyling M et al. Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;32:298-308.

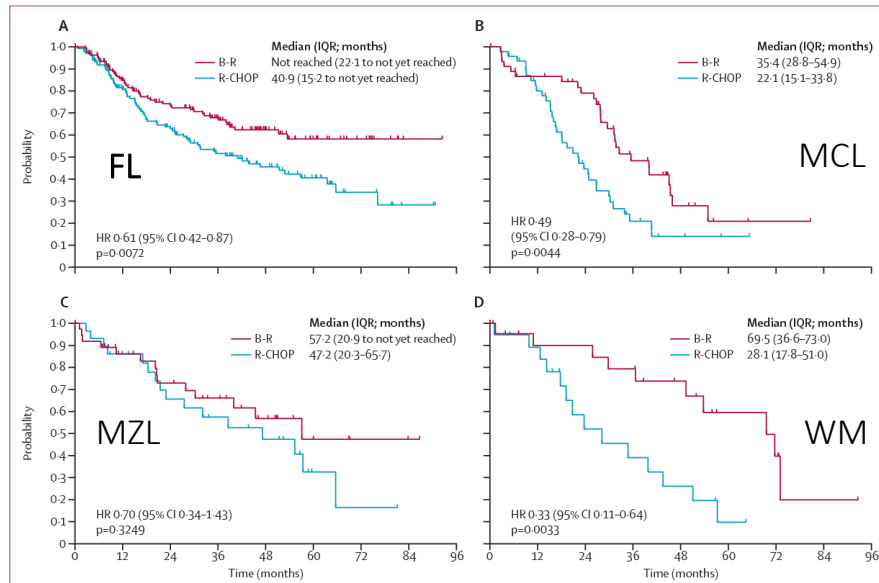
Treatment of advanced disease: what happened after Rituximab introduction?

Chemotherapy (CHOP, CVP, MCP, CHVP) plus Rituximab prolongs survival – HR 0.63 (95% CI 0.51-0.69)

Impact of chemotherapy regimen

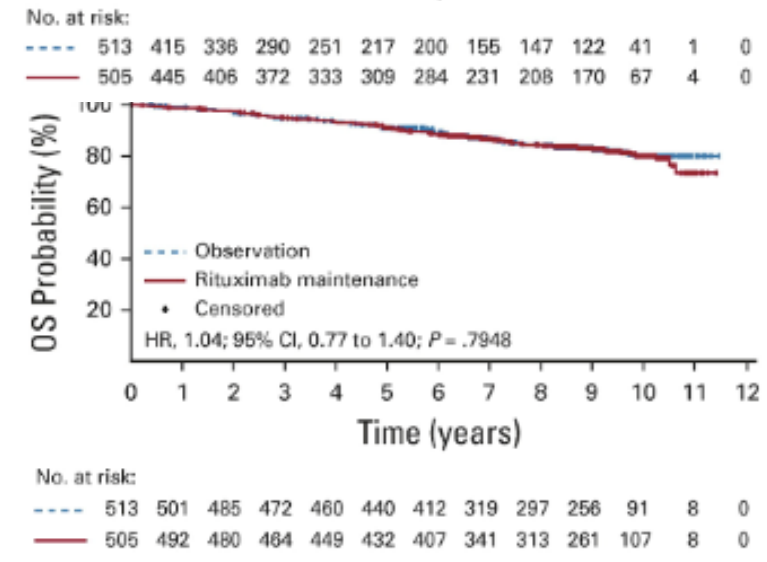
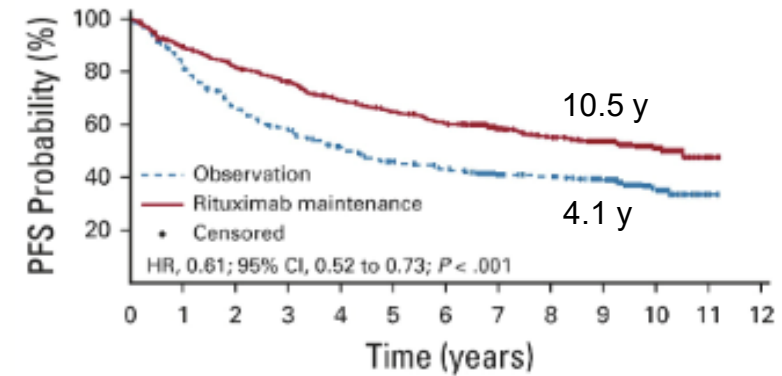


Luminari et al. J Clin Oncol. 2018 Mar 1;36(7):689-696



Rummel, M., et al. *The Lancet* 2013, 381, 1203-1210.

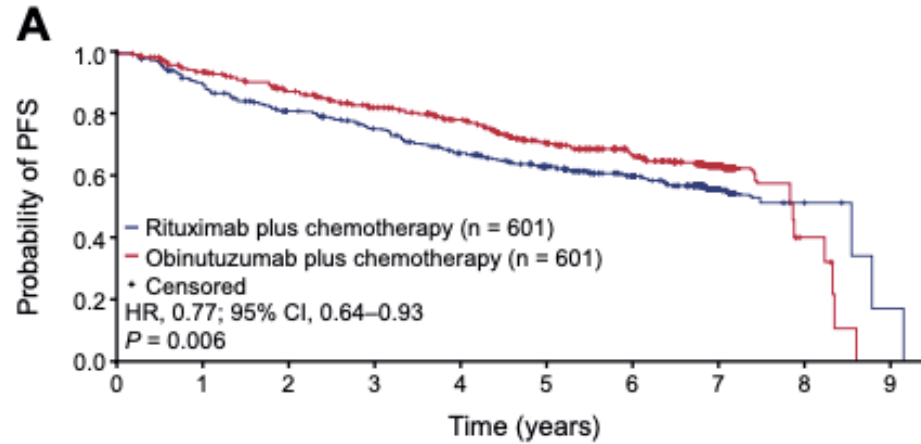
Impact of maintenance in responders: the PRIMA trial



Bachy E et al. J Clin Oncol. 2019 Nov 1;37(31):2815-2824

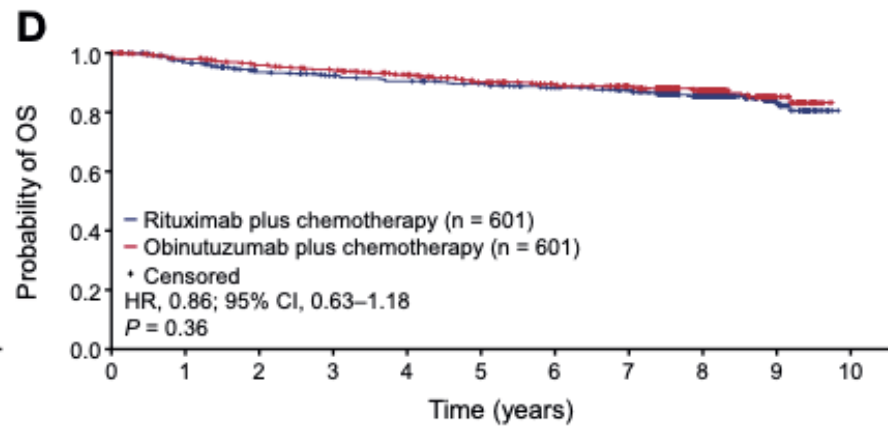
Treatment of advanced disease: what happened after Rituximab introduction?

Impact of different anti CD20 moAb: the GALLIUM study



No. of patients at risk

| | | | | | | | | | | | | | | | | | | | |
|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|---|
| | 601 | 563 | 512 | 471 | 447 | 430 | 405 | 375 | 351 | 333 | 314 | 290 | 266 | 239 | 157 | 28 | 5 | 3 | 1 |
| — | 601 | 574 | 541 | 514 | 493 | 469 | 449 | 433 | 409 | 375 | 349 | 322 | 297 | 264 | 167 | 27 | 5 | 1 | |

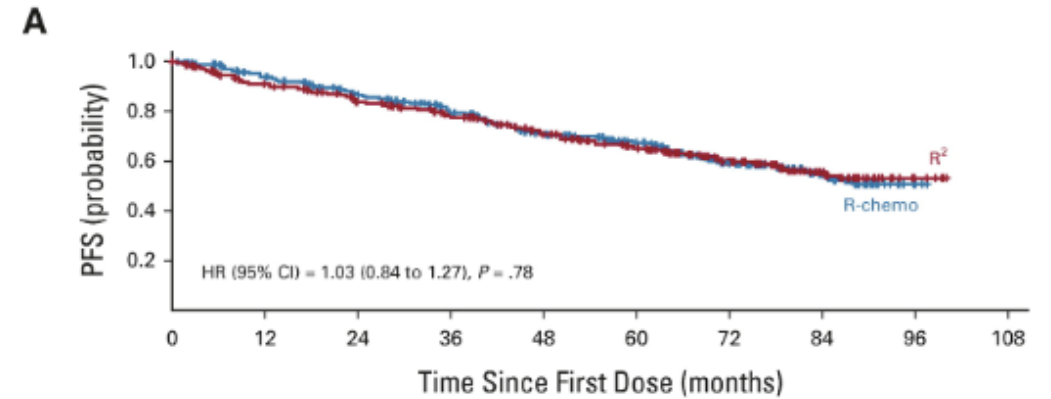


No. of patients at risk

| | | | | | | | | | | | | | | | | | | | | |
|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| | 601 | 588 | 566 | 550 | 533 | 527 | 517 | 510 | 504 | 495 | 489 | 479 | 473 | 468 | 452 | 375 | 260 | 163 | 80 | 20 |
| — | 601 | 584 | 573 | 564 | 551 | 542 | 533 | 524 | 518 | 504 | 495 | 489 | 482 | 474 | 444 | 372 | 257 | 146 | 64 | 13 |

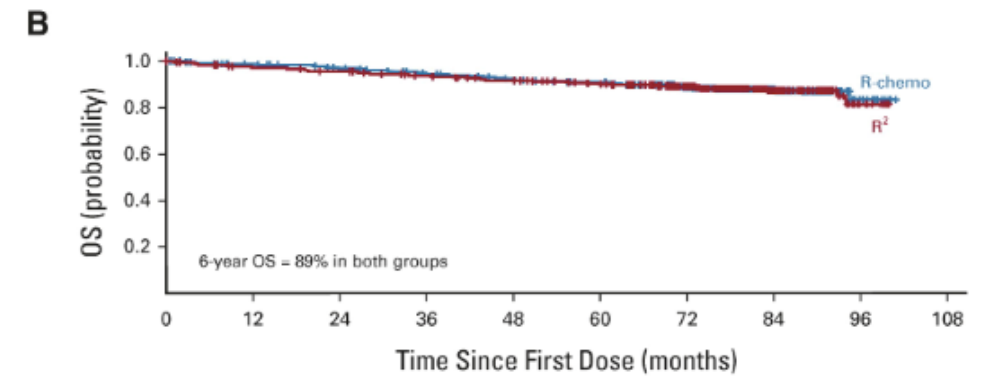
Townsend W ET AL. Hemasphere. 2023 Jun 30;7(7):e919

Rituximab Lenalidomide as 1L treatment: the RELEVANCE trial



No. at risk:

| | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| R-chemo | 517 | 446 | 390 | 333 | 277 | 243 | 146 | 56 | 3 | 0 |
| R ² | 513 | 412 | 370 | 328 | 281 | 242 | 157 | 51 | 5 | 0 |



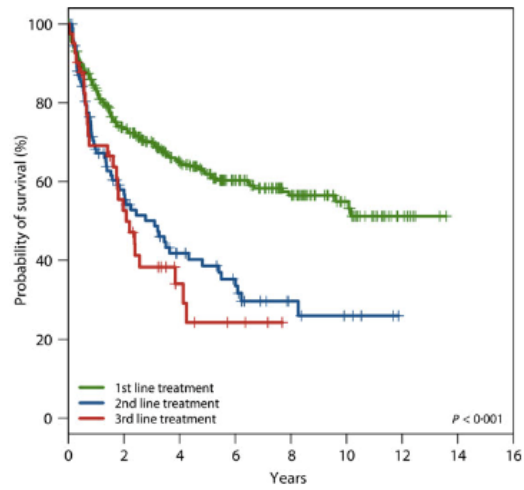
No. at risk:

| | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|----|---|
| R-chemo | 517 | 487 | 471 | 451 | 435 | 424 | 330 | 130 | 13 | 0 |
| R ² | 513 | 490 | 479 | 461 | 447 | 425 | 343 | 137 | 13 | 0 |

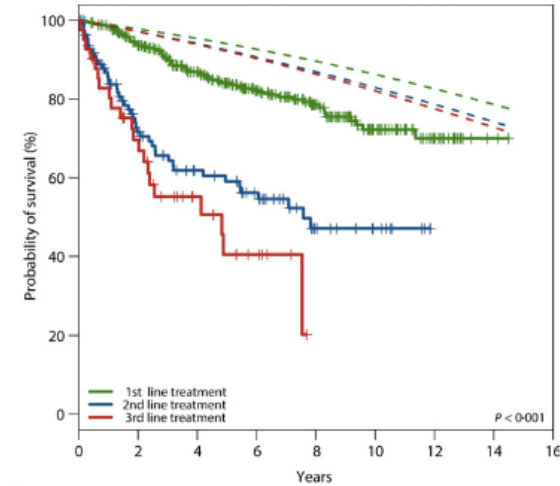
Morschhauser F et al, J Clin Oncol 2022, <https://doi.org/10.1200/JCO.22.00843>



Expected clinical course

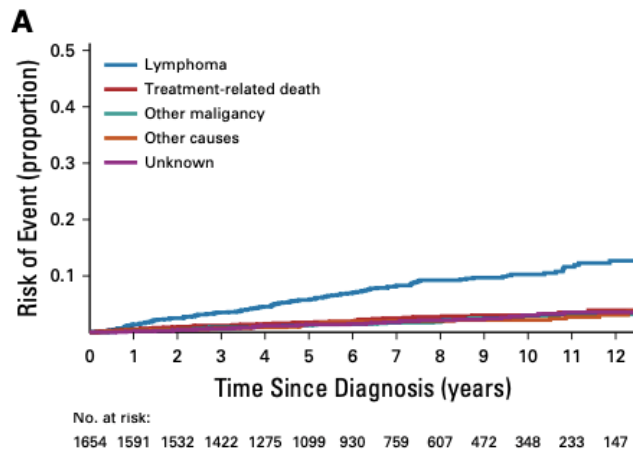


| No. at risk: | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
|--------------------|-----|-----|-----|-----|----|----|----|----|----|
| 1st line treatment | 348 | 210 | 148 | 100 | 62 | 31 | 7 | 0 | 0 |
| 2nd line treatment | 111 | 47 | 27 | 20 | 8 | 5 | 0 | 0 | 0 |
| 3rd line treatment | 41 | 19 | 7 | 3 | 0 | 0 | 0 | 0 | 0 |

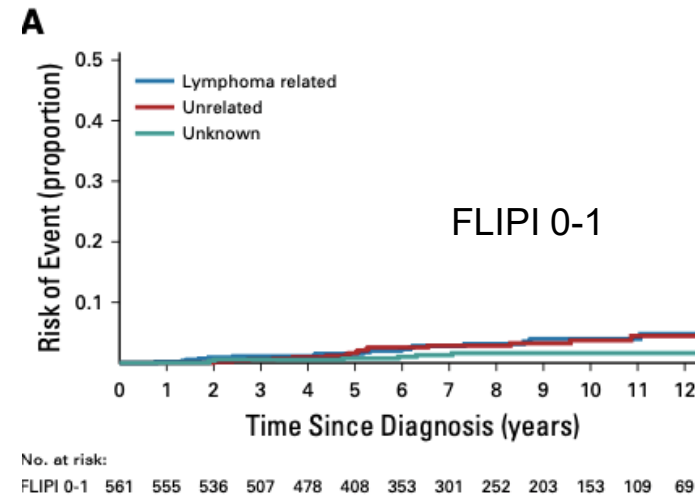


| No. at risk: | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
|--------------------|-----|-----|-----|-----|-----|----|----|----|----|
| 1st line treatment | 348 | 294 | 220 | 157 | 106 | 54 | 21 | 3 | 0 |
| 2nd line treatment | 111 | 62 | 45 | 35 | 14 | 8 | 0 | 0 | 0 |
| 3rd line treatment | 41 | 25 | 12 | 6 | 0 | 0 | 0 | 0 | 0 |

Rivas-Delgado A et al. Br J Haematol. 2019 Mar;184(5):753-759.



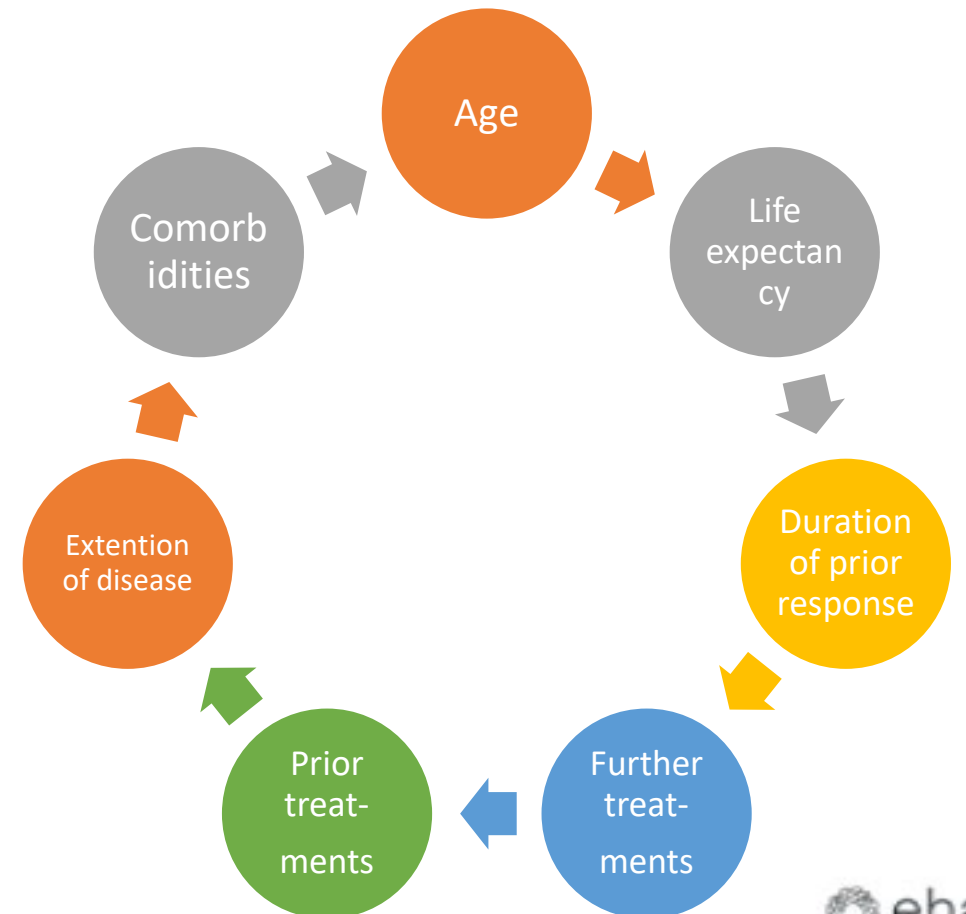
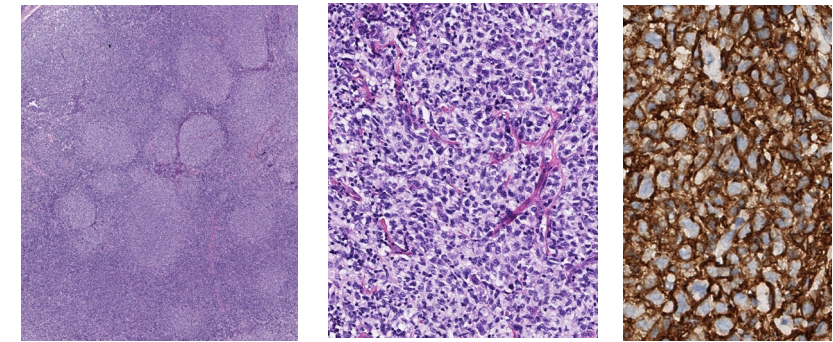
Sarkosy et al, J Clin Oncol. 2019 Jan 10;37(2):144-152



Challenges in the treatment of RR FL

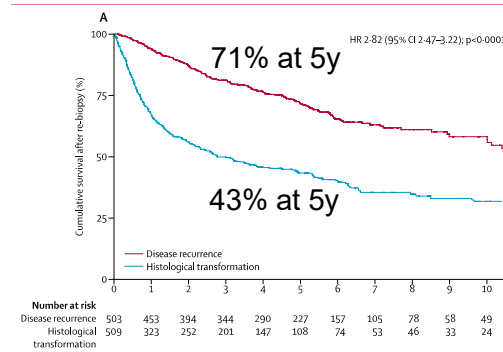
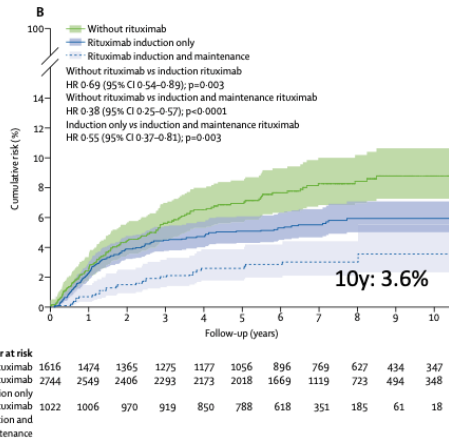
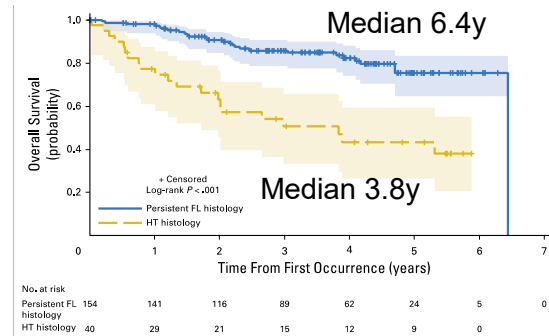
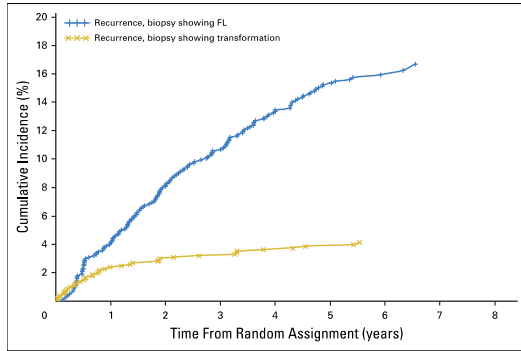
- Has **transformation** occurred?
 - ⇒ Always **repeat biopsy at relapse** (if possible PET guided)
- Which is the optimal **sequence of treatments**?
 - Mostly phase 2 trials at relapse
 - Heterogeneous populations in trials
 - No evaluation of treatment sequencing
- What are the **short and long term toxicities** of available options?
- How does treatment **choices impact further treatments**?

Personalize treatment

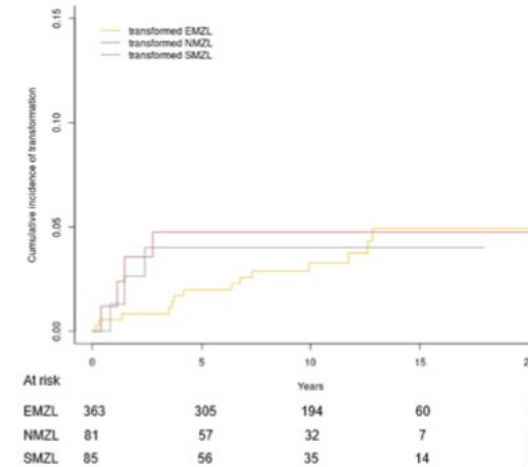


Transformation of indolent lymphomas

Follicular Lymphoma



Marginal Zone Lymphoma



Cumulative incidence of

- At 5y: 2.7% (5% in meta-analysis of 6 studies)
- At 10y: 3.6% (8% in meta-analysis of 6 studies)

HR for death: 3.96 (95% CI 2.06-7.55)

Risk factors: ≥ 2 EN sites, MALT IPI ≥ 2

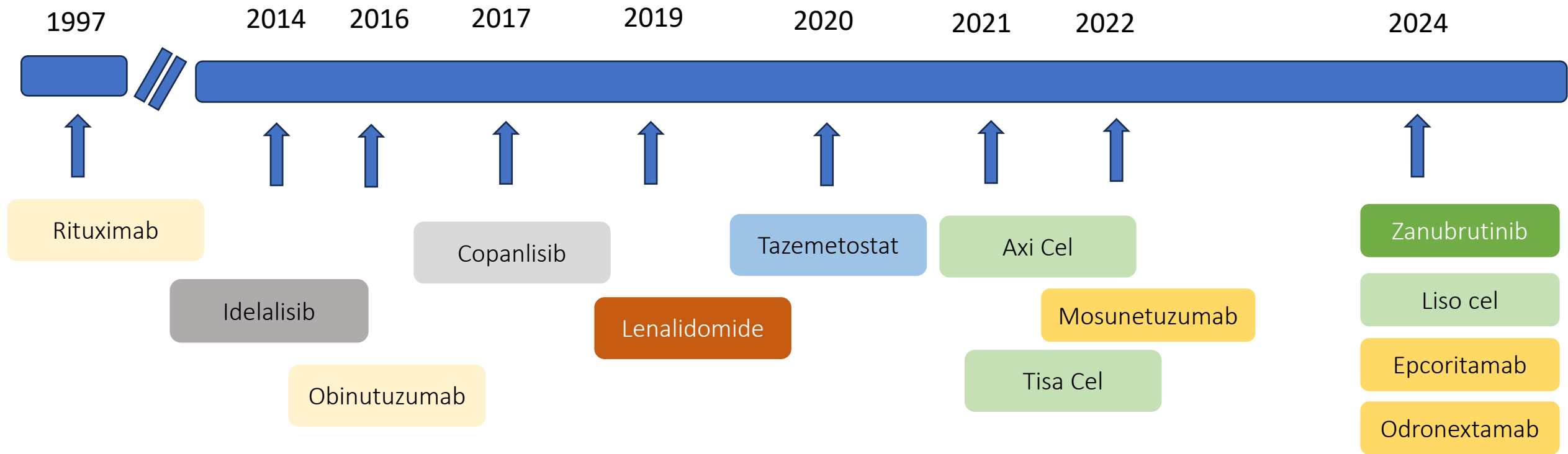
Sarkozy et al, *J Clin Oncol* **2016**, DOI: 10.1200/JCO.2015.65.7163

Federico et al, *Lancet Hematology* 2018, doi.org/10.1016/S2352-3026(18)30090-5

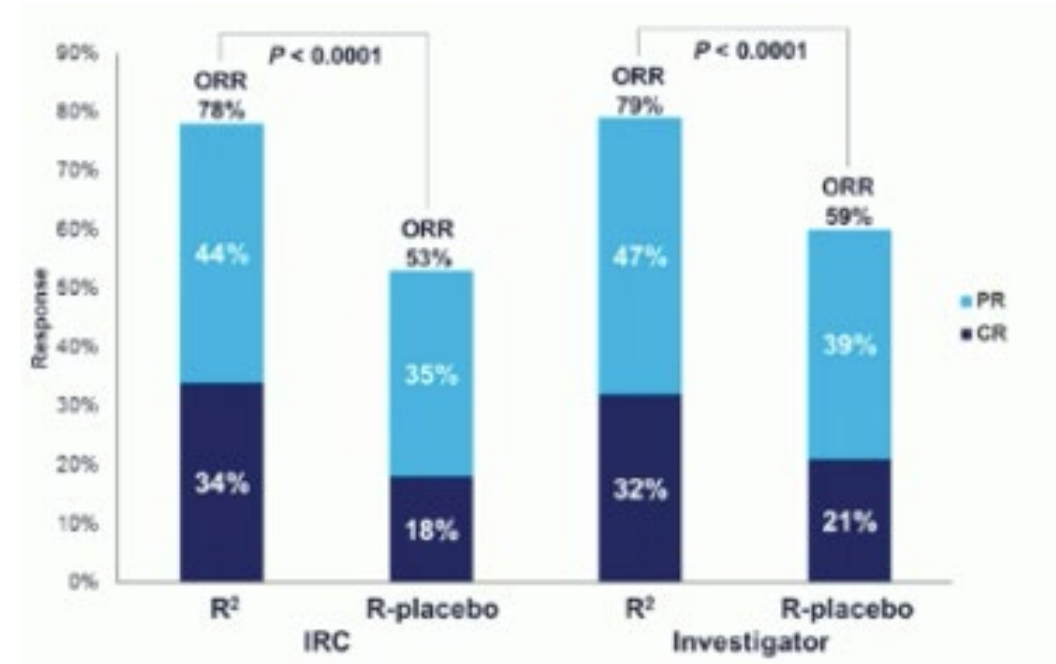
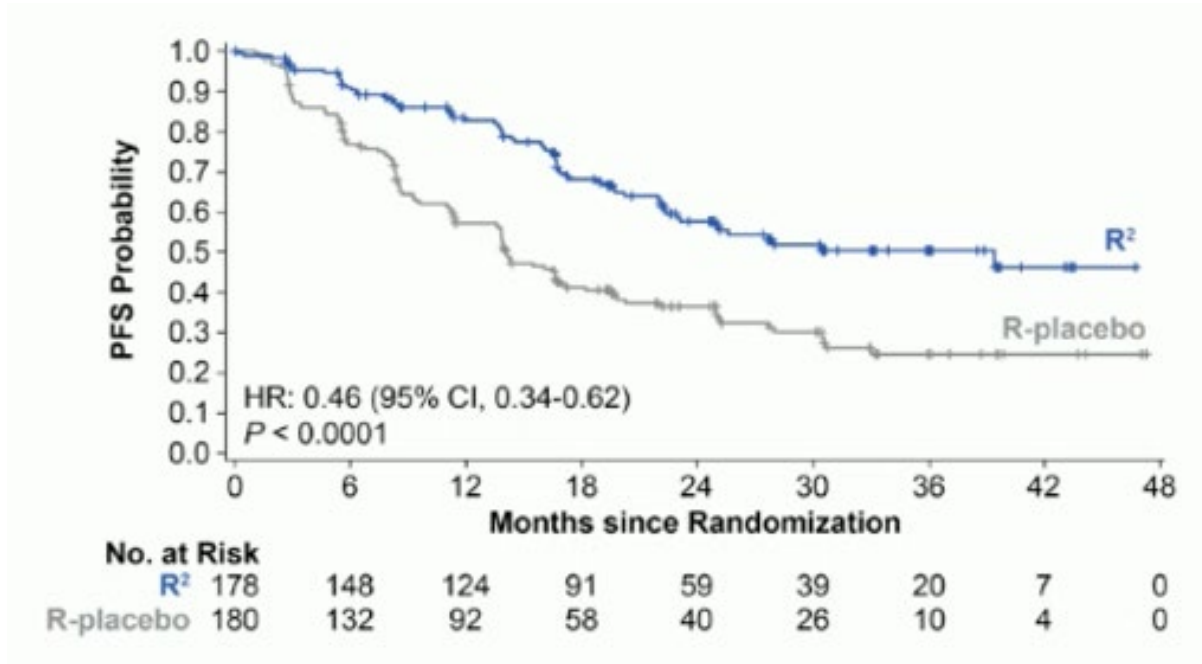
Bommier C et al. *Blood Adv.* 2024 Sep 25: bloodadvances



Non-chemotherapy options are growing for FL



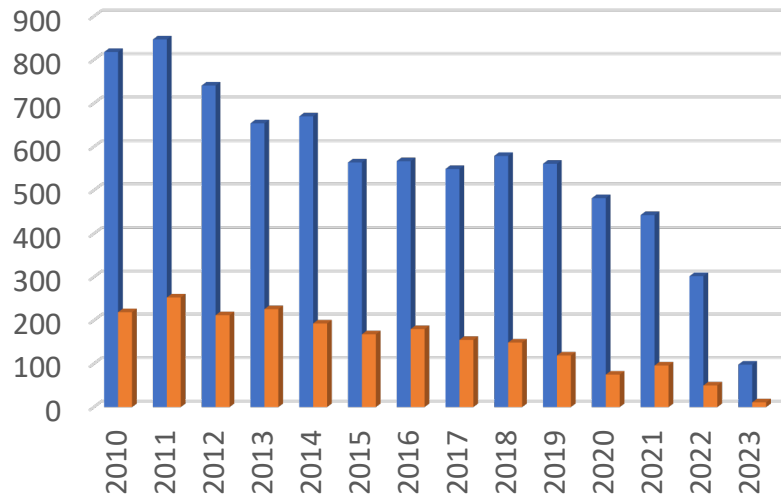
AUGMENT trial: Rituximab Lenalidomide improve PFS (and OS) in RR FL



Leonard JP et al. J Clin Oncol. 2019;37:1188-99.

Is there a role for transplant in relapsed refractory FL patients?

Follicular Lymphoma



■ Auto-HCT ■ Allo-HCT

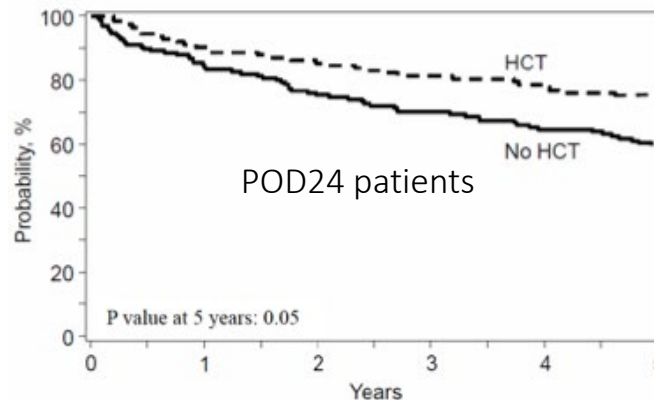
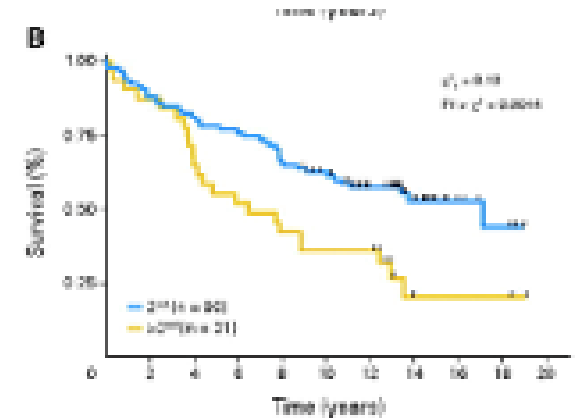
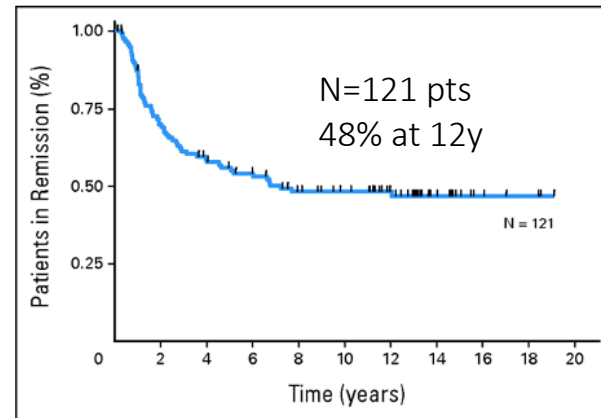
Auto-HCT
(2010-2022)

Allo-HCT
(2010-2022)

- 75.2%

- 63.1%

ASCT



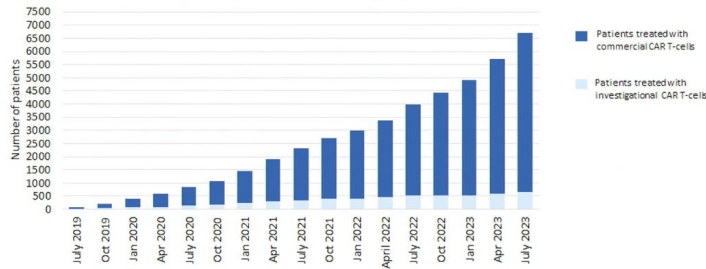
N= 174 ETF patients from NLCS
N= 379 ETF patients from CIBMTR

Rohatiner A et al, J Clin Oncol 2007 Jun 20;25(18):2554-9
Casulo C et al, Biol Blood Marrow Transplant. 2018 Jun;24(6):1163-1171..

CAR Ts for Follicular Lymphoma: updated follow up of three phase 2 trials

CAR T cell activity reported to EBMT*

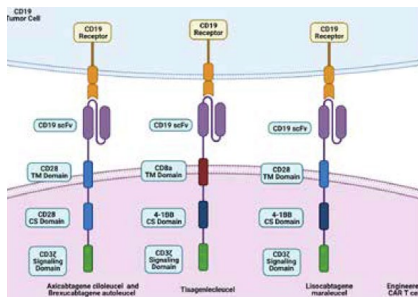
Number of CAR T-cell treated patients registered in the EBMT Registry



Source: EBMT Registry, July 2023

*Patients identified and marked with a CAR T-cell treatment, having at least minimal data on the diagnosis and treatment.

*increased by 27% in 2022; variable between countries



Wells D et al, *J Hematol Oncol Pharm.* 2022;12(1):30-42

Neelapu S et al, *Blood* 2024, 143 (6):496-506

Dreyling M et al, *Blood* 2024 doi: 10.1182/blood.2023021567.

Morschhauser F et al, *ICML 2023, LBA4*

| | ZUMA 5 (n=127 pts), FU 40m | ELARA (n=97 pts) FU 29m | TRANSCEND FL 001 (n=124 pts) FU 16.6-17.5m |
|--------------------------------------|-------------------------------|----------------------------|--|
| Age | 60 (34-79) | 57 (29-73) | 62 (23-80) |
| Male | 59% | 66% | 64% |
| Stage III-IV | 86% | 85.6% | 88% |
| FLIPI \geq 3 | 44% | 60% | 57% |
| Bulky | 51% (GELF) | 65% | 53% (GELF) |
| Prior lines, median (range) | 3 (1-10) | 4 (2-13) | 3 (2-10) |
| Refractory to last treatment line | 69% | 78% | 67% |
| POD24 | 56% | 63% | 43% |
| Prior ASCT | 24% | 36% | 31% |
| Prior Bendamustine | 69% | --- | |
| Received bridging | 4% | 45% | 38% |
| CRS G \geq 3 | 7% | 0% | 1% |
| ICANS G \geq 3 | 15% | 1% | 2% |
| ORR | 94% | 86% | 97% |
| CR | 79% | 68% | 94% |

ELARA – long term results with Tisa Cel

Median FU 29 mo

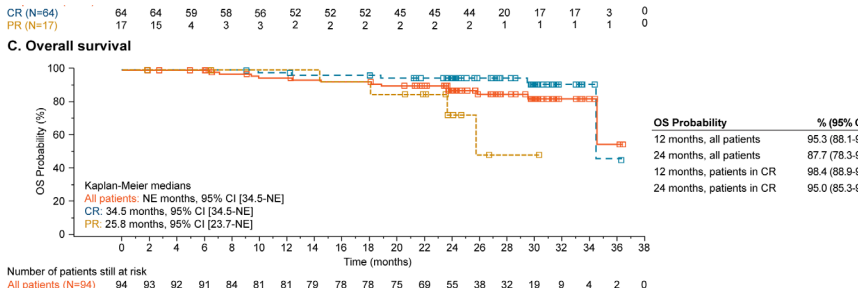
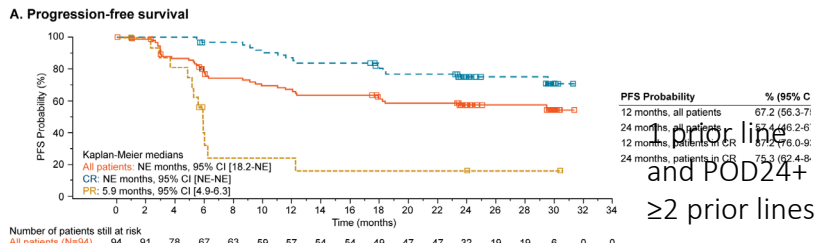


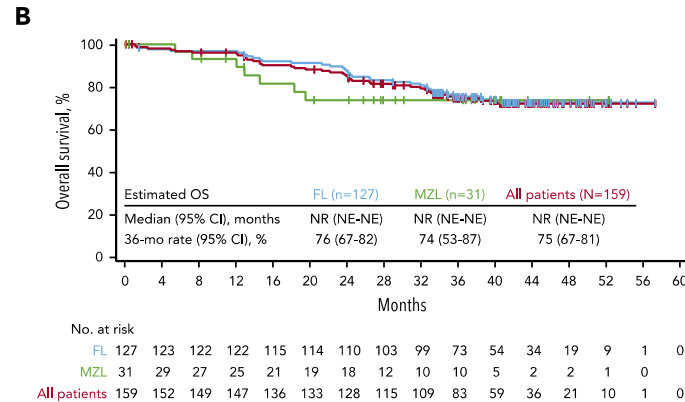
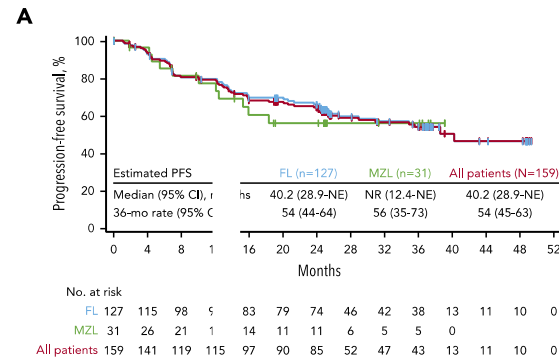
Figure 1



Dreyling M et al, Blood 2024 doi: 10.1182/blood.2023021567

ZUMA 5 – long term results with Axi Cel

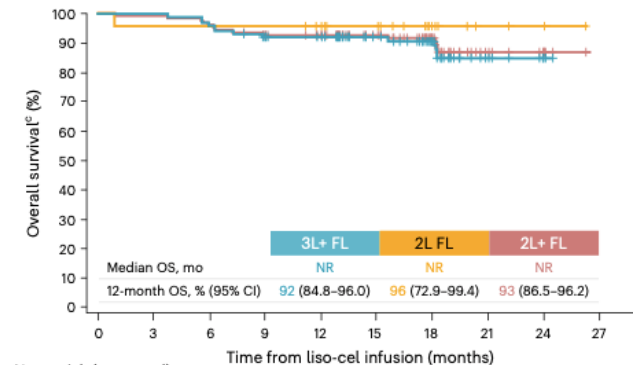
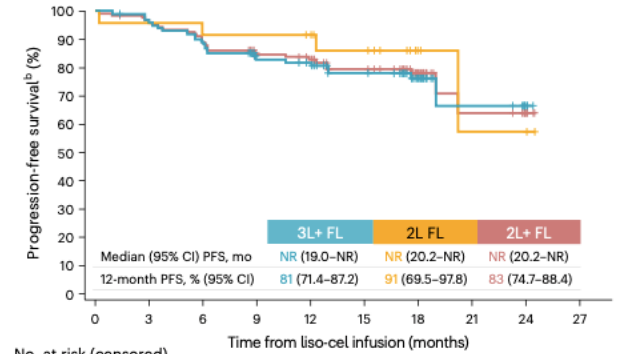
Median FU 40 mo



Neelapu S et al, Blood 2024, 143 (6):496-506

TRANSCEND FL – results with Liso Cel

Median FU 17.5- 17.8 mo



Morschhauser F et al, Nat Med 2024, 30: 2199-2207



CD3-CD20 bispecific antibodies approved for Follicular Lymphoma

| | Mosunetuzumab (n=90) (median FU 36 mo)* | Odronextamab (n=128) (median FU 20.1 mo)** | Epcoritamab (n=128) (median FU 17.4 mo)*** |
|---|--|---|---|
| Age | 60 (53-67) | 61 (22-84) | 65 (55-72) |
| % Male | 61 | 53 | 62% |
| % Stage III-IV | 77 | 85 | 91 |
| % FLIPI 3-5 | 44.4 | 58 | 51 |
| Bulky | --- | 14 | 20 (> 6cm) |
| Median prior lines | 3 (2-4) | 3 (2-13) | 3 (2-4) |
| % Prior ASCT | 21 | 30 | 19 |
| % POD 24 | 52 | 49 | 42 |
| % 1ary refractory/refractory to last treatment line | /69 | /72 | 54/69 |
| % ORR/CR | 78/60 | 80/72 | 82/62 |
| DoR/ DoCR mo | 35.9/NR | 21.7/25 (17.7-NR) | 52.2%/78.4% at 18m |
| PFS mo | 24 mo | 20.7 (16.7-26.5) | 15.5 mo (49% and 74% PSF at 18m for ORR/CR) |
| OS | NR | NR | NR (70% at 18 m) |
| % CRS | 44% (G≥3 2.2%) | 56% (G≥3 1.7% step up dosing) | 66% (G≥3 2%) |
| % ICANS | 39 (G≥3 3%) | 1 pt (G<3) | 6% (G≥3 0%) |

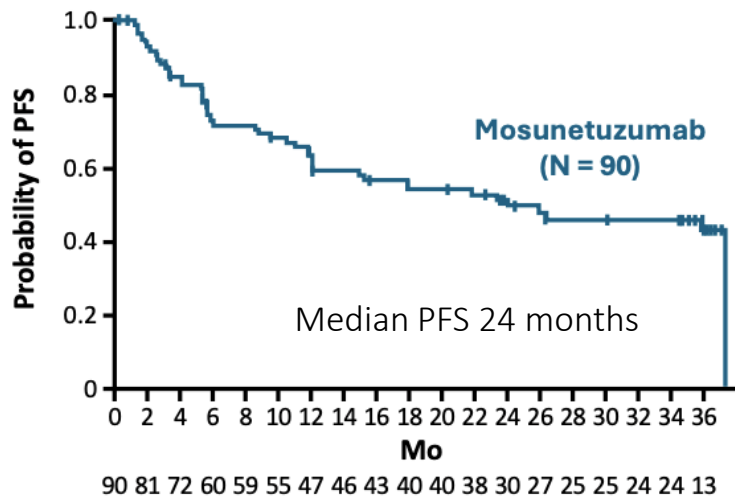
* Budde Lancet Oncol 2022; Schuster ASH 2023 abst 603

**Kim TM et al. Ann Oncol 2024,
doi.10.1016/j.annonc.2024.08.2239

***Linton K et al. Lancet Hematol 2024, 11: e593

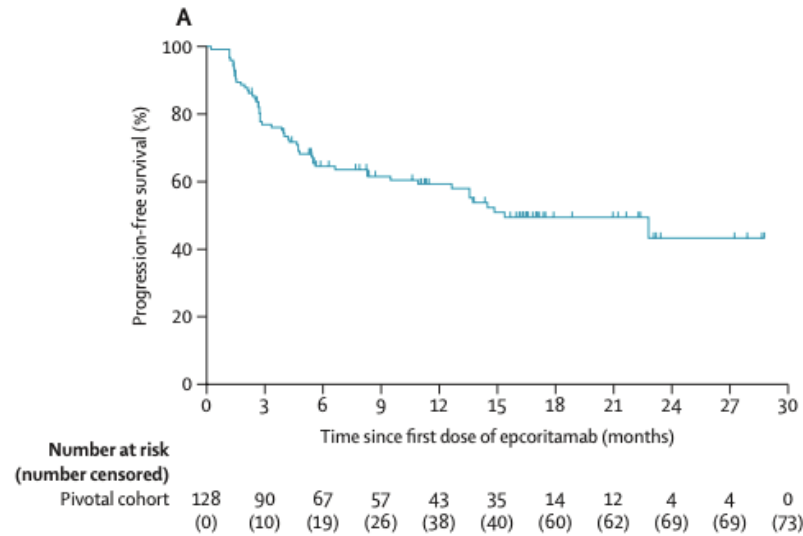
Assessment of long term outcomes will need prolonged follow up

Mosunetuzumab



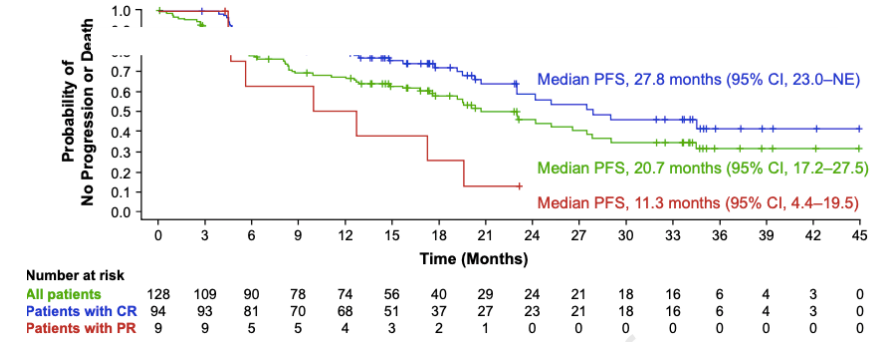
36 month follow up

Epcoritamab



17.4 month follow up

Odronextamab



20.1 month follow up

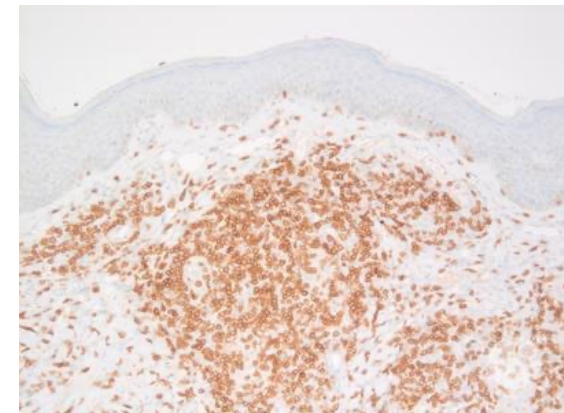
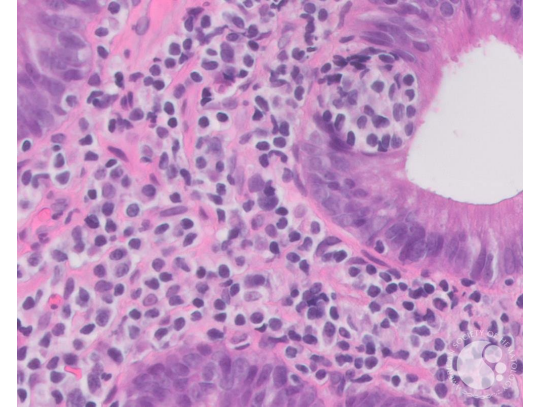
Schuster. ASH 2023. Abstr 603.

Kim TM et al. Ann Oncol 2024, doi.10.1016/j.annonc.2024.08.2239

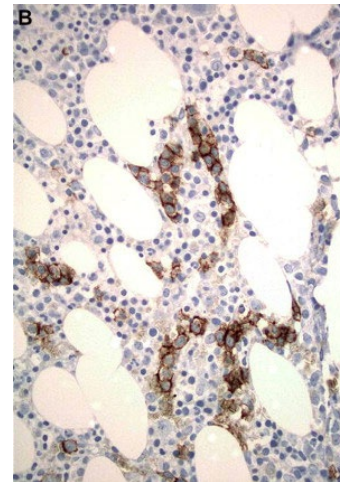
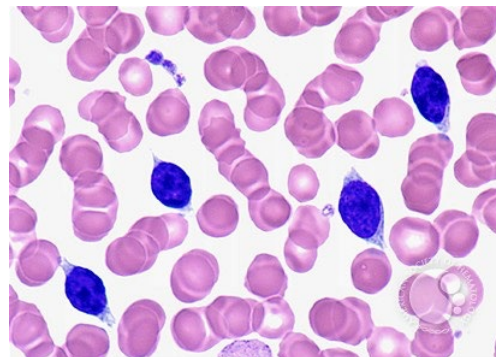
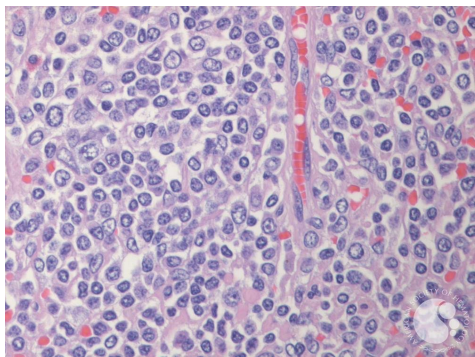
Linton K et al. Lancet Hematol 2024, 11: e593

Marginal zone lymphomas: different entities under the same name

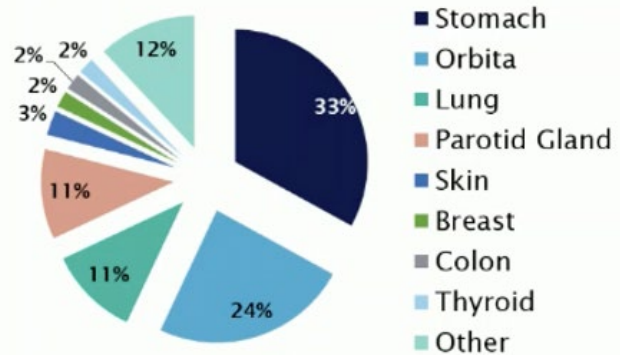
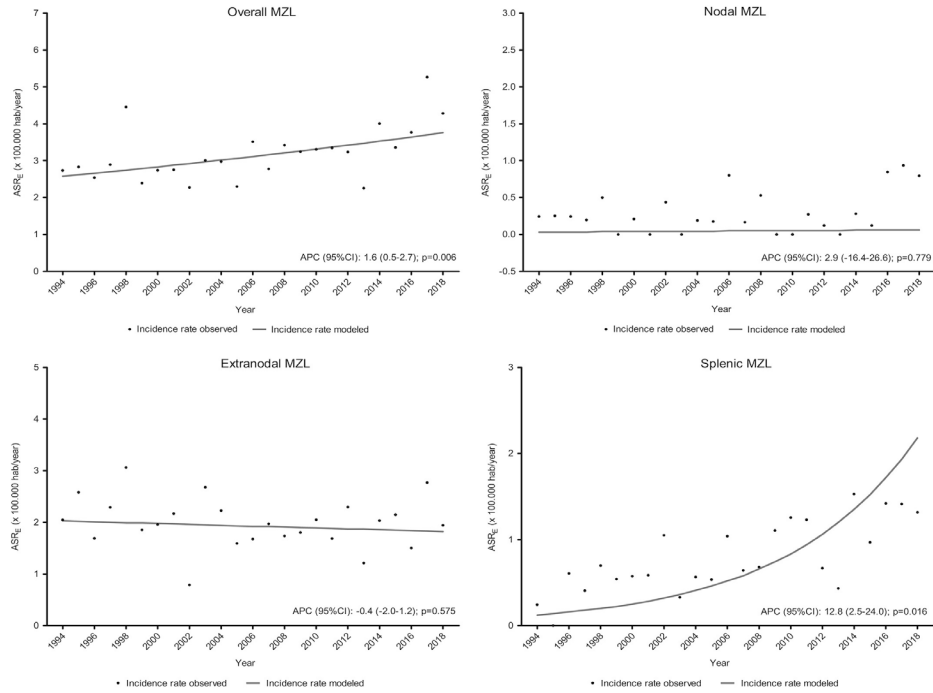
| ICC 2022 | WHO 5th Editions (2022) | Revised WHO 4th (2016) |
|---|---------------------------------------|-----------------------------------|
| Extranodal MZL (MALT) 50-70% | Extranodal MZL (MALT) | Extranodal MZL (MALT) |
| Splenic MZL 20% | Splenic MZL | Splenic MZL |
| Nodal MZL <10% | Nodal MZL | Nodal MZL |
| Pediatric nodal MZL (provisional) | Pediatric nodal MZL (distinct entity) | Pediatric nodal MZL (provisional) |
| Primary cutaneous MZ lymphoproliferative disorder | Primary cutaneous MZL | (not considered as an entity) |



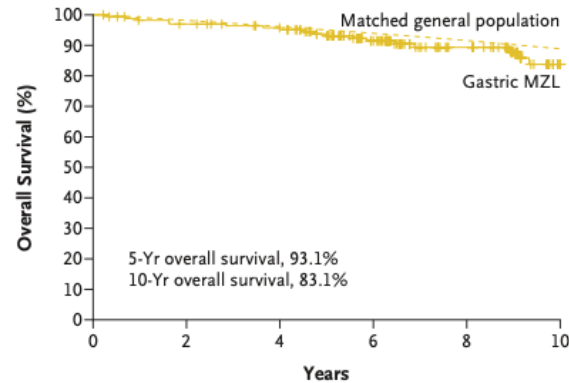
Zucca et al, *Hematological Oncology*. 2023;41(S1):88–91.



Incidence and outcomes of MZL

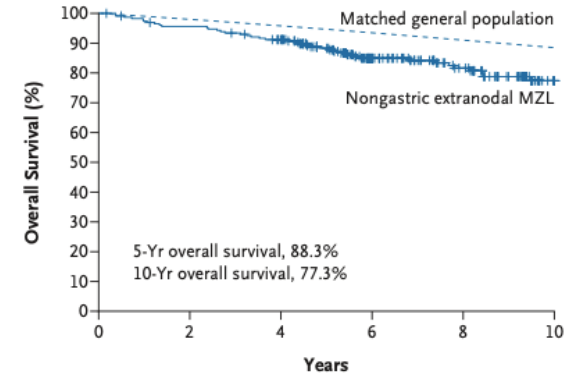


A Gastric MZL

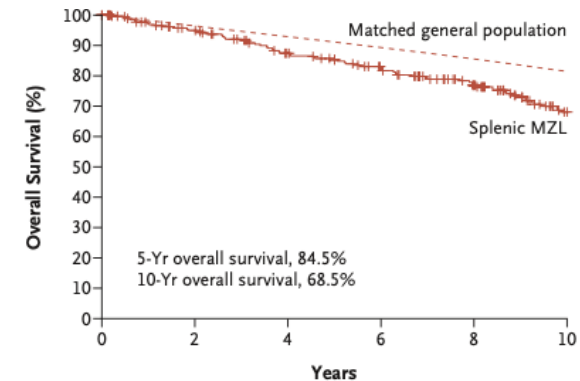


| No. at Risk | 171 | 160 | 151 | 108 | 67 | 30 |
|-----------------------|-------|------|------|------|------|------|
| Relative Survival (%) | 100.0 | 98.6 | 98.9 | 97.3 | 97.0 | 94.0 |

B Nongastric Extranodal MZL



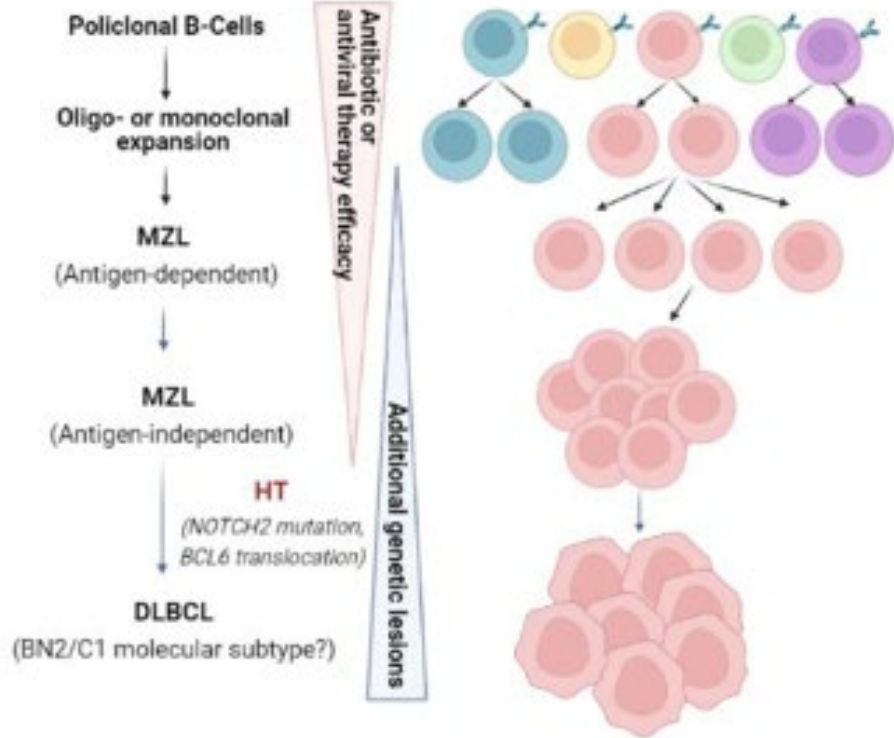
| No. at Risk | 230 | 217 | 201 | 129 | 92 | 42 |
|-----------------------|-------|------|------|------|------|------|
| Relative Survival (%) | 100.0 | 96.9 | 95.1 | 90.8 | 89.6 | 87.4 |



| No. at Risk | 265 | 230 | 198 | 176 | 146 | 102 |
|-----------------------|-------|------|------|------|------|------|
| Relative Survival (%) | 100.0 | 96.9 | 92.1 | 90.4 | 87.9 | 82.1 |

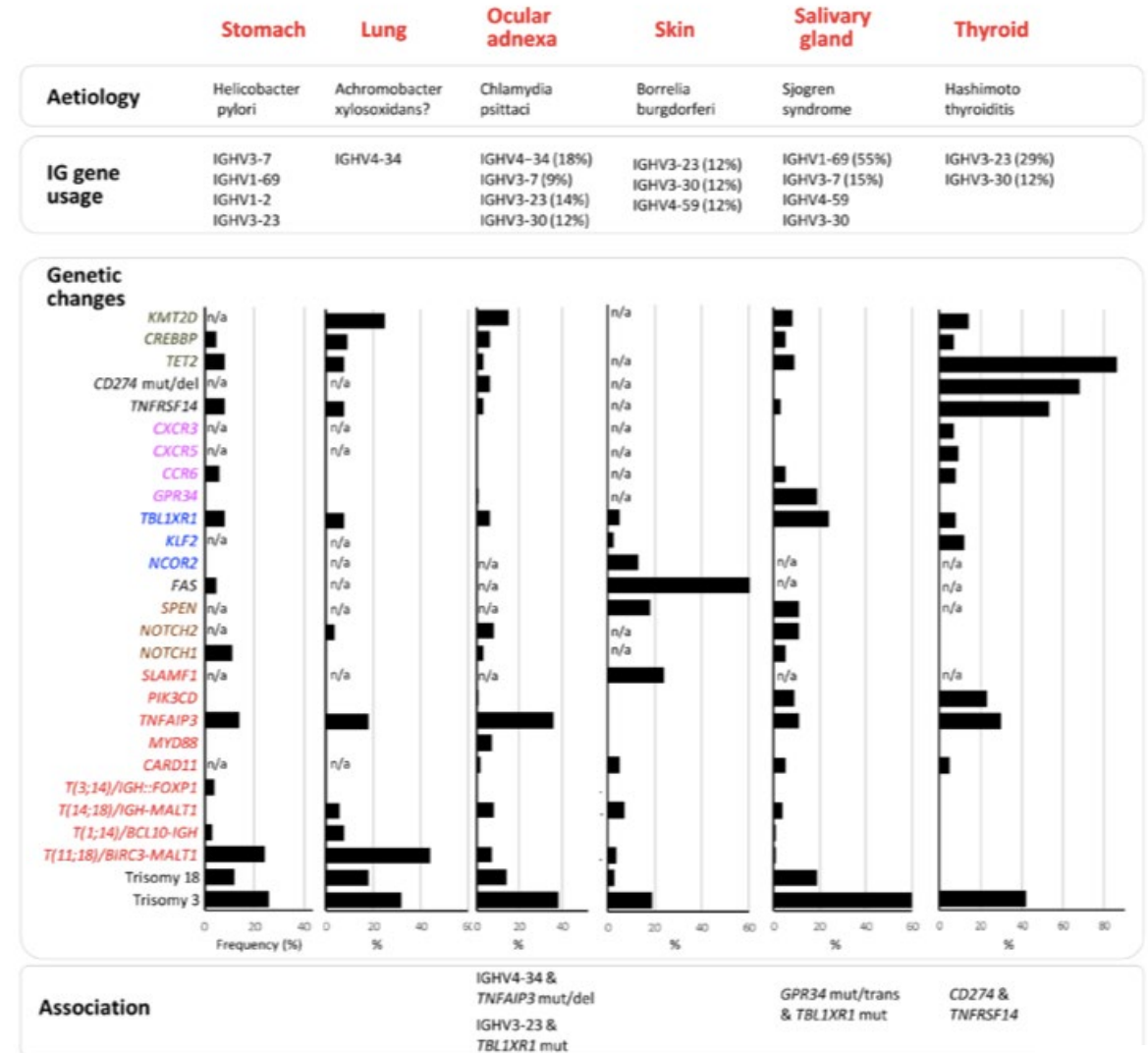
Rossi D et al. N Engl J Med 2022;386:568-81

Pathogenesis of ENMZL



A. Proposal of antigen-driven MZL pathogenesis

EMZL at various mucosal sites



Diagnosis is not always straightforward

Nodal and extra nodal MZL

Other indolent B NHL

- Lymphoplasmacytic lymphoma/Waldenstrom's Macroglobulinemia
- CLL/SLL
- Follicular lymphoma
- Mantle cell lymphoma

Clinical picture

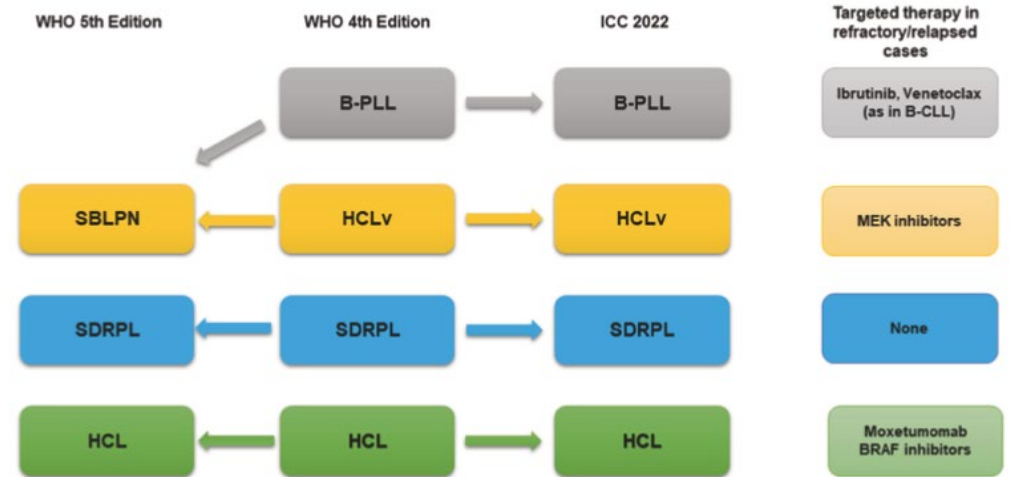
IgM paraprotein

Morphology

Immuno phenotype

MYD88^{L265P} mutation

SMZL



Falini B et al, Leukemia (2023) 37:18–34; <https://doi.org/10.1038/s41375-022-01764-1>

Morphology, immunophenotype and molecular characteristics

Staging and prognostic assessment

Staging:

Lab evaluation

- Microbiological assessment
- Autoimmune serologies (Sjorgren S)

Imaging

- CT scan
- PET CT?

Organ specific procedures

- Upper GI endoscopy
- MRI (orbital, salivar)

- **BM** morphology
- BM phenotype (except ENMZ?)

MALT IPI¹

Age > 70 anos

Stage III/IV

LDH > UNL

Risk

Low : 0 factors

Intermediate: 1 factor

High: ≥2 factors

Splenic MZL³

Hb < 9.5 g/dL

Platelets < 80 000/mcl

LDH > UNL

Extra hilar adenopathy

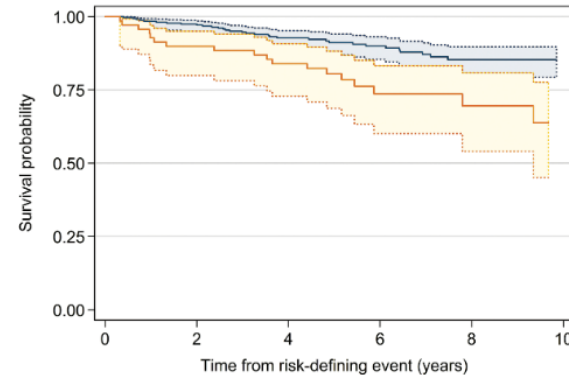
Risk

Low : 0 factors

Intermediate 1-2 factors

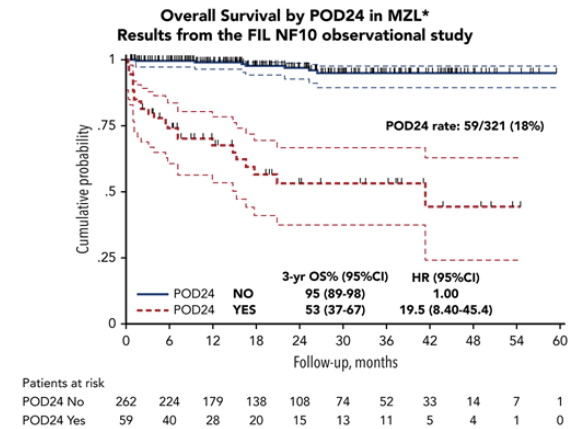
High 3-4 factors

POD24²



MALT pts receiving systemic treatment

NF10 study⁴



¹Thieblemont C et al. Blood 2017, 130(12): 1409-1417

²Conconi A et al. Haematologica. 2020 Nov 1;105(11):2592-2597

³Montalban C et al. Leuk Lymphoma. 2014 Apr;55(4):929-31

⁴Luminari S et al. Blood. 2019 Sep 5;134(10):798-801.

Treatment depends on pathogenesis, symptoms, extension and location

Localized EMZL (70%)

H Pylori eradication

Other antibiotics,
Hepatitis C treatment

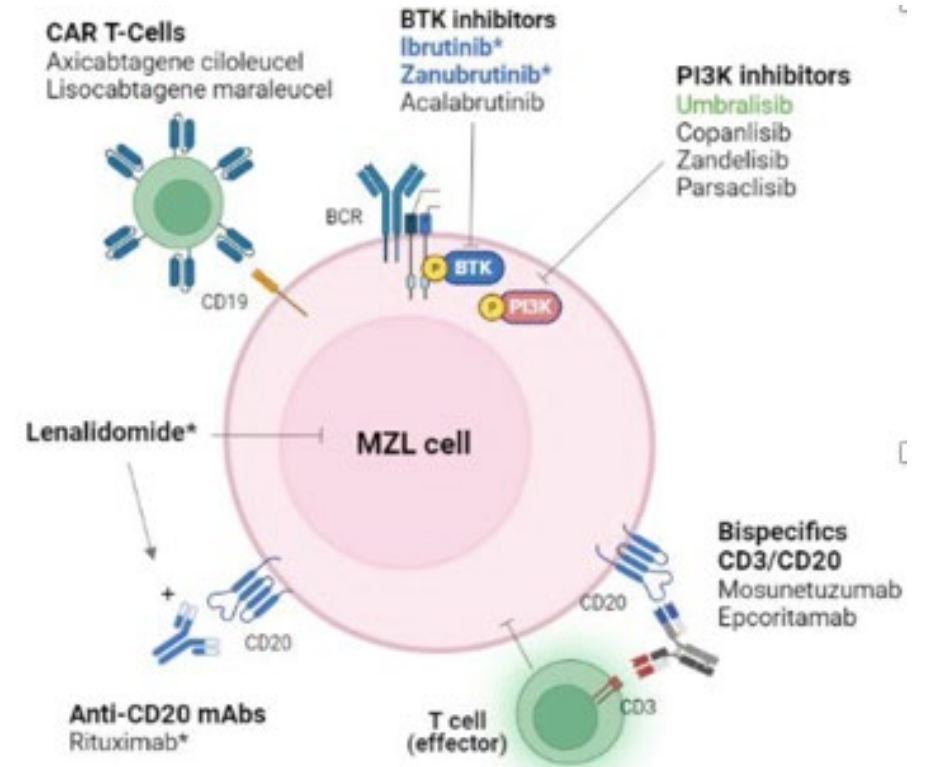
Local therapy
(Surgery,
Radiotherapy)

Systemic approaches

Watch and wait

Immunochemotherapy

Immunomodulators
BTK inhibitors

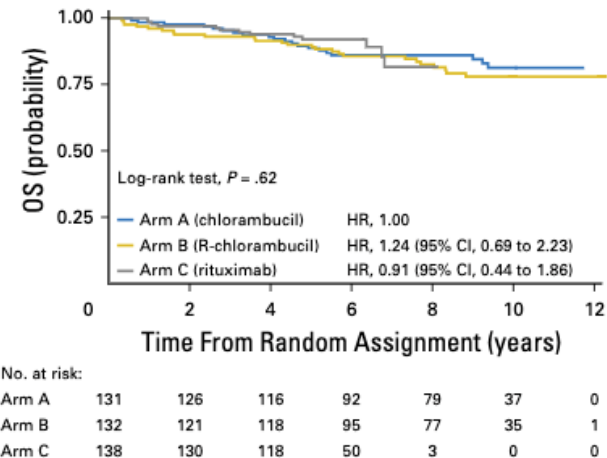
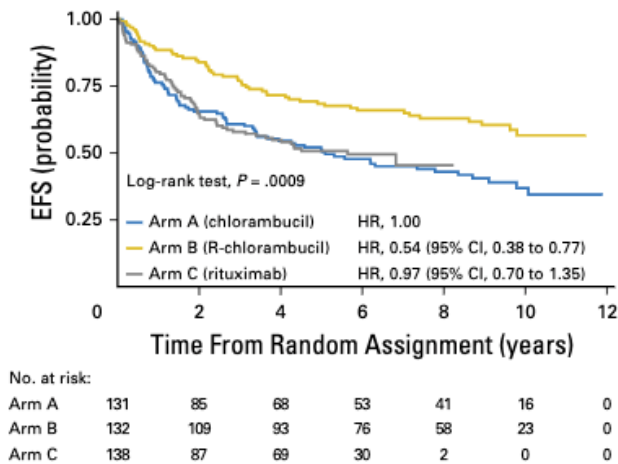


Zucca E et al, Ann Oncol 2020, 31: 17 – 29
 Broccoli A and Zinzani PL Hematology 2020, DOI 10.1182/hematology.2020000157
 Walewska R et al. Br J Haematol 2024, 204: 86-107
 Rossi D and Zucca E. N Engl J Med 2022;386:568-81

Merli M, Arcaini L. ASH Educational Session 2022

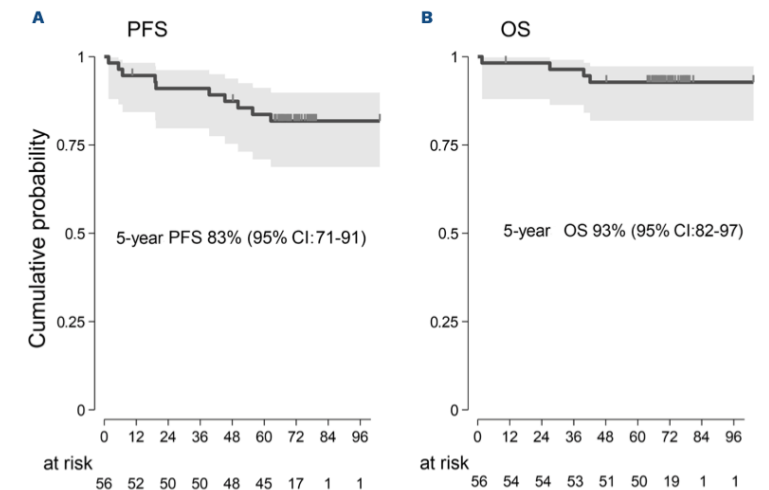
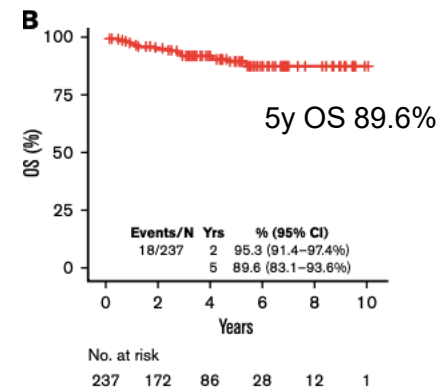
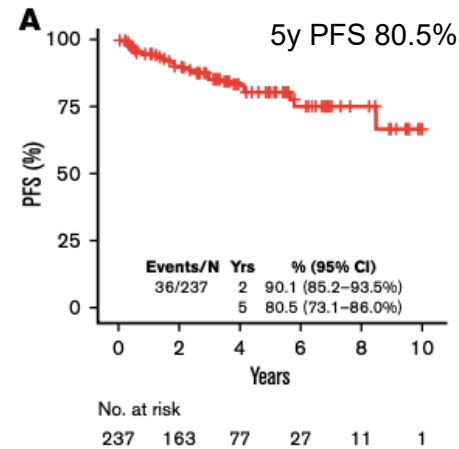
Systemic treatment for advanced disease: is there a standard?

IELSG 19: Rituximab Chlorambucil



Zucca E et al. J Clin Oncol. 2017 Jun 10;35(17):1905-1912

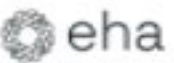
Bendamustin Rituximab



Alderuccio P et al. Blood Adv 2022, DOI 10.1182/bloodadvances.2021006844.

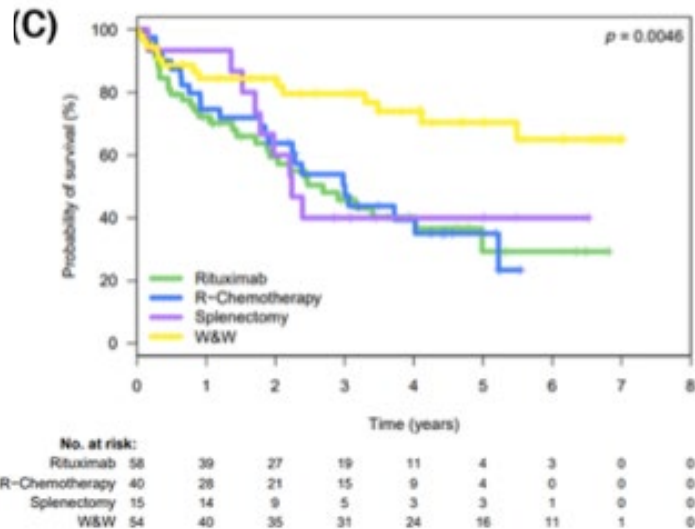
Iannitto et al, Br J Haematol. 2018 Dec;183(5):755-765

Iannitto et al, Haematologica 2024, <https://doi.org/10.3324/haematol.2023.28410>



When and how to treat splenic marginal zone lymphoma?

Median **time to first treatment**: 58 mo (at 10y 30% remain untreated) ⇒ treat if symptomatic
 (Perrone et al, Hematol Oncol 2015)



Muntanola A et al. Br J Haematol. 2023 Aug;202(4):776-784.

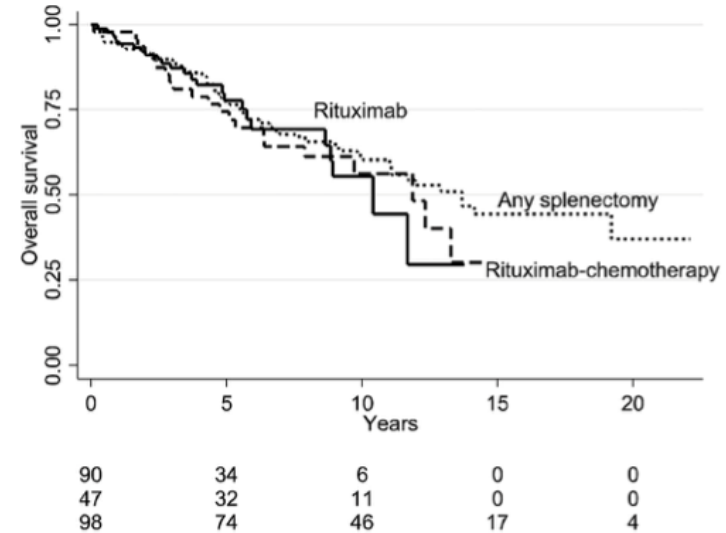
Rituximab 375 mg/m² weekly x 6 → maintenance for 1 year
 Kalpadakis C et al, Blood. 2018;132(6):666–70.

Rituximab Bendamustine x 6 cycles (BRSMA)
 Kalpadakis C et al, Blood. 2018;132(6):666–70.

ORR 92%
 CR 44%
 10y PFS 64%
 10y OS 85%

ORR 91%
 CR 73%
 3y PFS 90%
 3y OS 96%

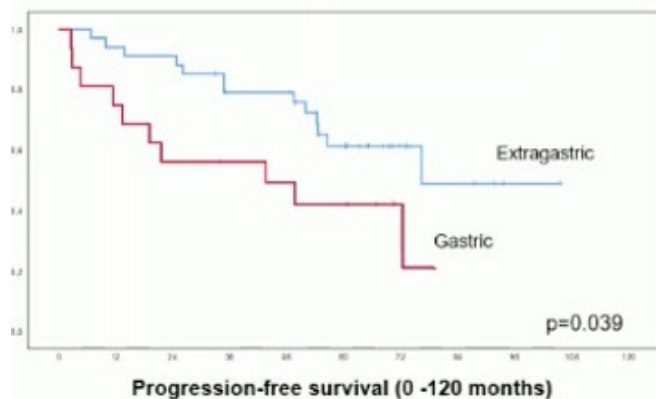
≥G3 Neutropenia 43%
 Infections 5.4%
 SAE 25%



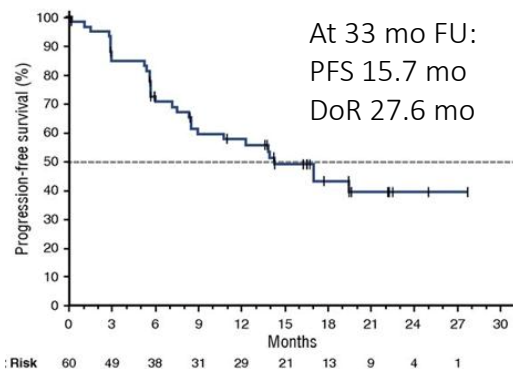
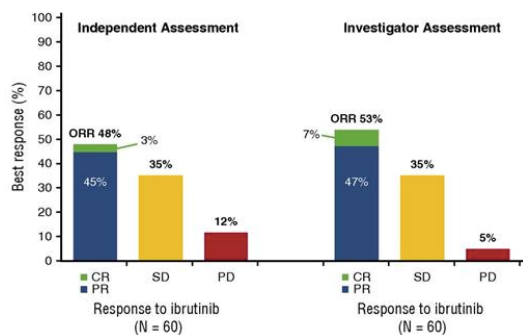
Julen HR et al. *eJHaem*. 2023;4:647–655.

Systemic treatment options for MZL: beyond immunochemotherapy

Long term FU of Lenalidomide in MALT lymphoma¹



Ibrutinib in R/R MZL (all subtypes)²

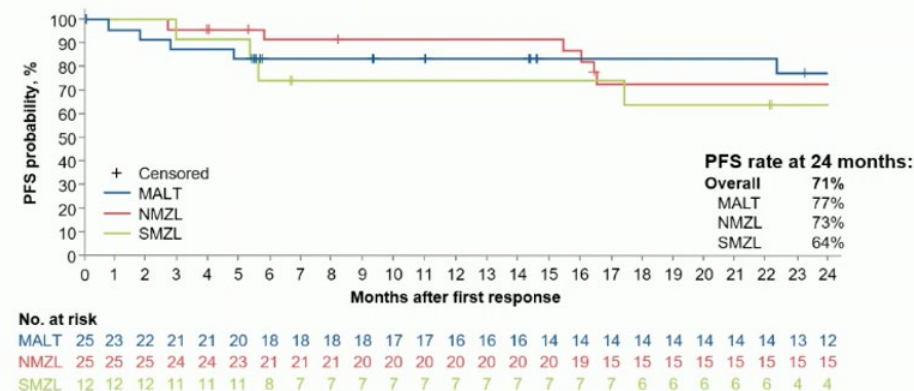


Zanubrutinib in R/R MZL: the MAGNOLIA trial³

| MZL subtype | Response | 2-Year Rates | | |
|------------------|--------------------------|-------------------|-----|-----|
| | | Response Duration | PFS | OS |
| Nodal (n = 25) | ORR 76% CR 20% PR 56% | 78% | 73% | 80% |
| Splenic (n = 12) | ORR 67% CR 8% ORR 58% | Not estimable | 64% | 92% |
| MALT (n = 25) | ORR 64% CR 40% PR 24% | 75% | 77% | 92% |

MAGNOLIA – Longer-Term Follow-Up

Median FU 27.4 mo

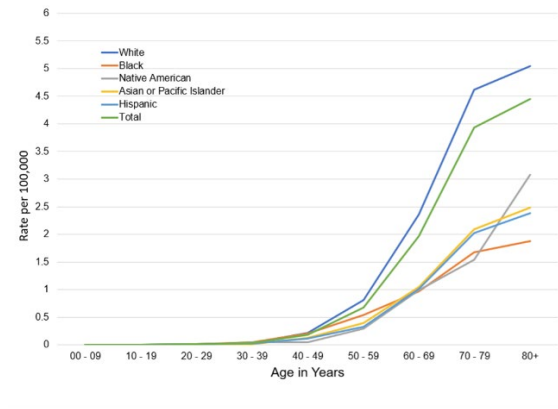
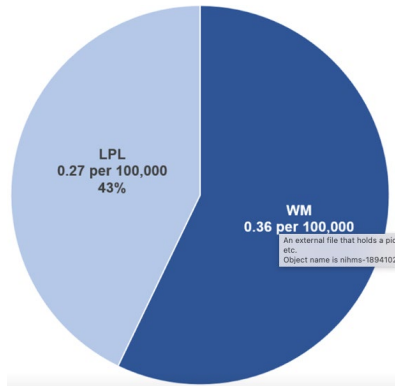


1. Kiesewetter et al. Hematol Oncol. 2019 Oct;37(4):345-351

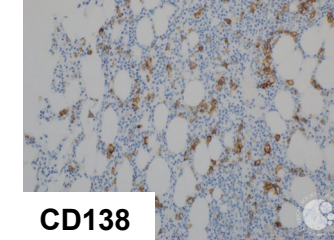
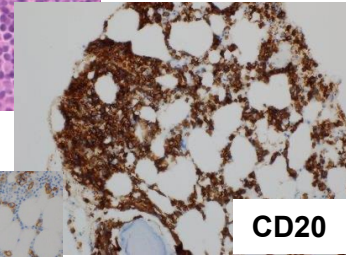
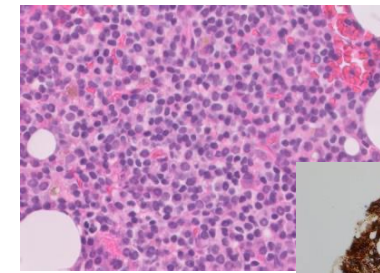
2. Noy A et al. Blood. 2017 Apr 20;129(16):2224-2232

3. Opat S et al. Blood Adv. 2023 Nov 28;7(22):6801-6811

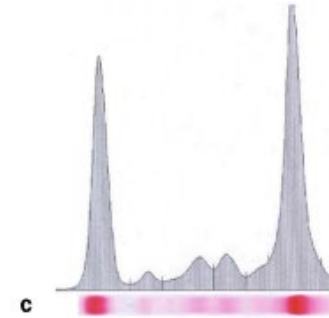
Waldenstrom's Macroglobulinemia



Median age: 70



ASH image bank



McMaster ML.
Semin Hematol 2023 Mar, 60(2):65-72

| Gene | Hunter Z et al [42] (N=30) | Poulain S et al [71] (N=98) | Poulain S et al [86] (N=125) | Varettoni M et al [56] (N=119)* | Jiménez C et al [84] (N=61)† | Global frequency (%) |
|----------|----------------------------|-----------------------------|------------------------------|---------------------------------|------------------------------|----------------------|
| MYD88 | 27 | 82 | 105 | 87 | 53 | 82 |
| CXCR4 | 8 | 24 | 30 | 15 | 22 | 23 |
| KMT2D | 2 | NA | NA | 19 | NA | 14 |
| CD79A/B | 2 | 12 | 10 | 4 | 5 | 7.6 |
| TP53 | 2 | NA | 9 | 10 | 2 | 6.9 |
| NOTCH2 | 1 | NA | NA | 8 | NA | 6 |
| ARID1A | 5 | NA | NA | 4 | 3 | 5.7 |
| HIST1H1E | 0 | NA | NA | NA | 4 | 4.4 |
| PRDM1 | 0 | NA | NA | 5 | NA | 3.4 |
| MYBBP1A | 2 | NA | NA | 0 | 3 | 2.4 |
| TRAF3 | 1 | NA | NA | 1 | 3 | 2.4 |
| TRAF2 | 1 | NA | NA | NA | 1 | 2.2 |
| RAG2 | 1 | NA | NA | NA | 1 | 2.2 |
| HIST1H1B | 0 | NA | NA | NA | 2 | 2.2 |
| HIST1H1C | 0 | NA | NA | NA | 2 | 2.2 |
| HIST1H1D | 0 | NA | NA | NA | 1 | 1.1 |

3 groups
 MYD88 mutated, CXCR4 wild type
 MYD88 mutated, CXCR4 mutated
 MYD88 wild type

Clinical findings are diverse

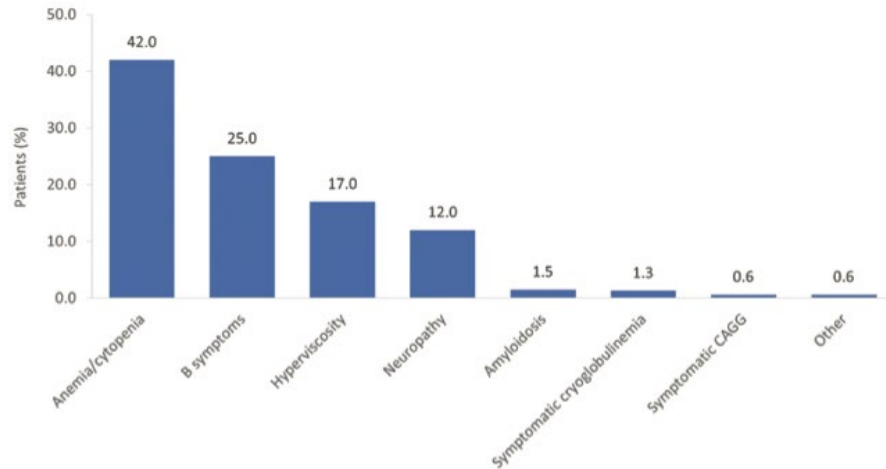
Symptoms and signs

Lymphoma related

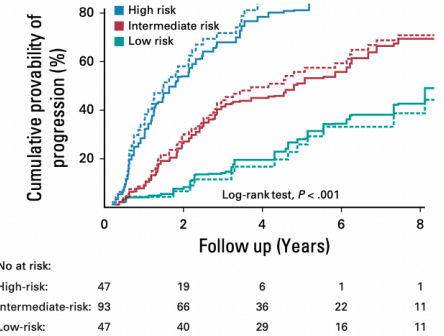
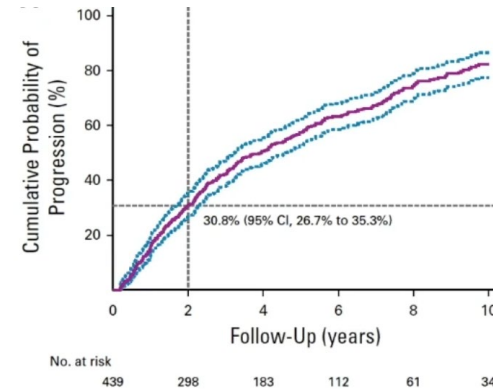
- Cytopenias
- Lymphadenopathy
- Hepatosplenomegaly
- B symptoms

IgM related

- Hyperviscosity
- Cryoglobulinemia
- Neuropathy
- Hemolysis
- Amyloidosis



19-28% patients are asymptomatic at diagnosis



At median FU 7.8 years: 72% pts progressed to symptoms

Risk factors for progression to treatment

BM infiltration > 70%
 Albumin < 3.5g/dL
 B2M ≥ 4mg/dL
 IgM > 4500 mg/dL

Low risk (TTPm 9.3 y)
Intermediate risk (TTPm 4.8 y)
High risk (TTPm 1.8 y)

First line treatment depends on symptoms and disease dynamics

Asymptomatic patients ⇒ observation

Hyperviscosity ⇒ plasmapheresis (while treatment is started)

Immunochemotherapy

Protesome inhibitor - based

BTK inhibitor - based

| Regimen | No prior treatment; relapsed refractory | ORR | Major response | Median PFS | Median OS | Toxicities |
|---|--|--------------------------|-----------------------|--------------------------------------|---------------------|--|
| **DRC ¹ | 72; 0 | 83% | 74% | 35 mo | 95 mo | |
| **DRC ² | 50; 50 | 1st L: 96% RR: 87% | 1st L: 87% RR: 68% | 1st L: 34 mo RR: 32 mo | NR | G≥3 Neutropenia 20% G≥3 Thrombocytopenia 7% G≥3 infections 3% |
| *R-Bendamustine ³ | 19;0 | NR | NR | 69,5 mo | NR | Infections, cytopenias, cutaneous rash, 2nd tumors |
| *R-Bendamustine ⁴ (n=257 evaluable)** | 257;0 | 92% | 88% | 65 mo | NR | |
| **Bortezomib- dexametasone Rituximab ⁴ | 59;0 | 85% | 68% | 42 mo (TTNT 73 mo) | 3y OS 81% | ≥G3 Peripheral neuropathy 7% |
| **Carfilzomib RD ⁵ | 31; 0 | 87% | 68% | 46 mo | NR | ≥G3 Peripheral neuropathy 3%, ≥G3 Cardiopathy 3% |
| **Ixazomib DR ⁶ | 26;0 | 96% | 77% | 40 mo | 100% at 52 mo FU | ≥G3 Peripheral neuropathy 4% |

* consider **4 cycles**

** consider deferring Rituximab if
risk of hyperviscosity

¹ Dimopoulos MA et al, J Clin Oncol (2007) 25:3344-3349. ⁴ Dimopoulos et al. Blood. 2013 Nov 7;122(19):3276-82

² Paludo J. et al BJH, 2017, 179, 98–105

³ Rummel MJ et al, Lancet 2013;381:1203- 10

⁴ Rummel et al Blood. 2019; 134(suppl 1):343.

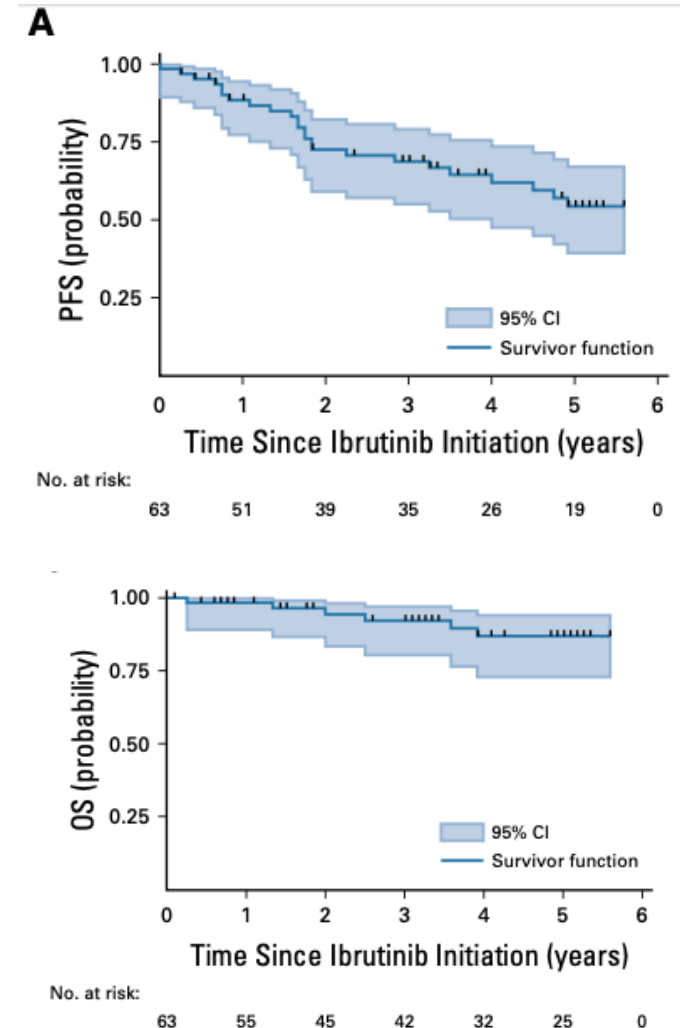
⁵ Treon et al. Blood. 2014;124(4):503-510.

⁶ Castillo J. et al Blood Adv. 2020 ,25;4(16):3952-3959

BTK inhibitors are very effective for WM: Ibrutinib

| Trial | Outcomes | Toxicity |
|---|--|--|
| Phase II, relapsed refractory n=63 Median 2 (1-9) prior therapies 40% refractory to prior T | Median FU 59mo ORR 90.5% MMR 79.4% PFS 2y 69.1% OS 2y 95.2% 5y 87% Time to Response 4 weeks | Grade ≥3AE: neutropenia (15.9%), thrombocytopenia .11,1% pneumonia (3.2%), AF 12.7% |
| Phase III refractory to Rituximab n=31 | Median FU 18.1mo ORR 90% MMR 71% PFS 18 mo 86% OS 18 mo 97% | Grade ≥3AE neutropenia 13%, HBP 10%, anemia, thrombocytopenia and diarrhea 6% |
| Phase II, treatment naive n=30 | Median FU 50mo ORR 100% MMR 87% PFS 4y 76% OS 4y 100% | Grade 2-4 AEs Fatigue (33%), upper respiratory tract infection (30%), hematoma (27%) AF and ITU (20%), HBP, lower RTI, rash (17%) |

Buske C et al. Leukemia (2023) 37:35–46

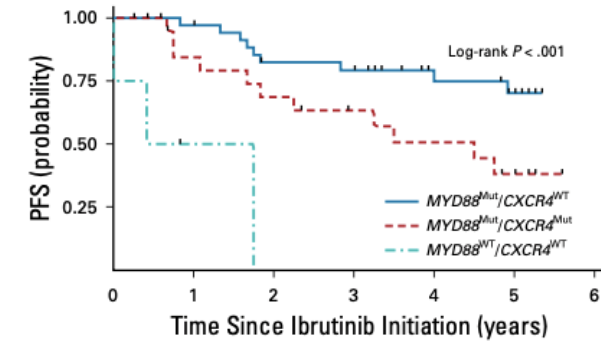


Impact of mutational profiles on response to Ibrutinib

| Variable | All patients | MYD88mut CXCR4wt | MYD88mut CXCR4mut | MYD88wt CXCR4wt |
|---------------------------------------|--------------|---------------------|----------------------|--------------------|
| No. pts | 63 | 36 | 22 | 4 |
| ORR | 57 (90.5%) | 36 (100%) | 19 (86.4%) | 2 (50%) |
| Major response (≥VGPR) | 50 (79.4%) | 35 (97.2%) | 15 (68.2%) | 0 |
| Minor response | 7 (11%) | 1 (2.8%) | 4 (18.2%) | 2 (50%) |
| No response | 6 (9.5%) | 0 | 3 (13.6%) | 2 (50%) |
| Time to major response (median) | 1.8 mo | 1.8 mo | 4.7 mo | NA |

Treon S et al. J Clin Oncol 2021, 39: 565-575.

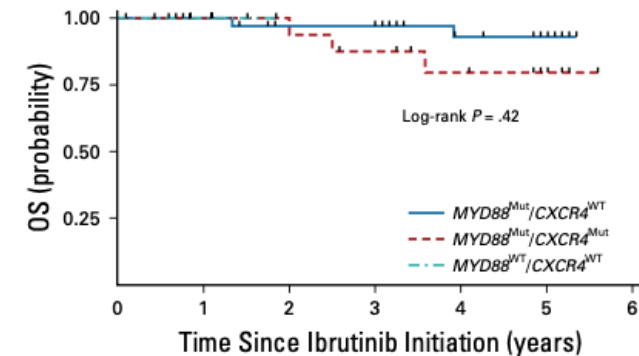
B



No. at risk:

| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|--|----|----|----|----|----|----|---|
| MYD88 ^{Mut} /CXCR4 ^{WT} | 36 | 34 | 26 | 25 | 18 | 14 | 0 |
| MYD88 ^{Mut} /CXCR4 ^{Mut} | 22 | 16 | 13 | 10 | 8 | 5 | 0 |
| MYD88 ^{WT} /CXCR4 ^{Mut} | 4 | 1 | 0 | 0 | 0 | 0 | 0 |

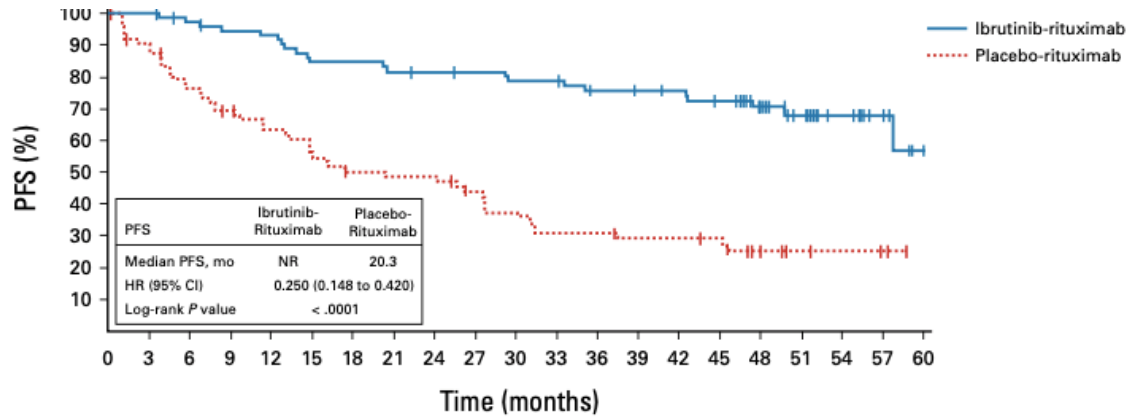
D



No. at risk:

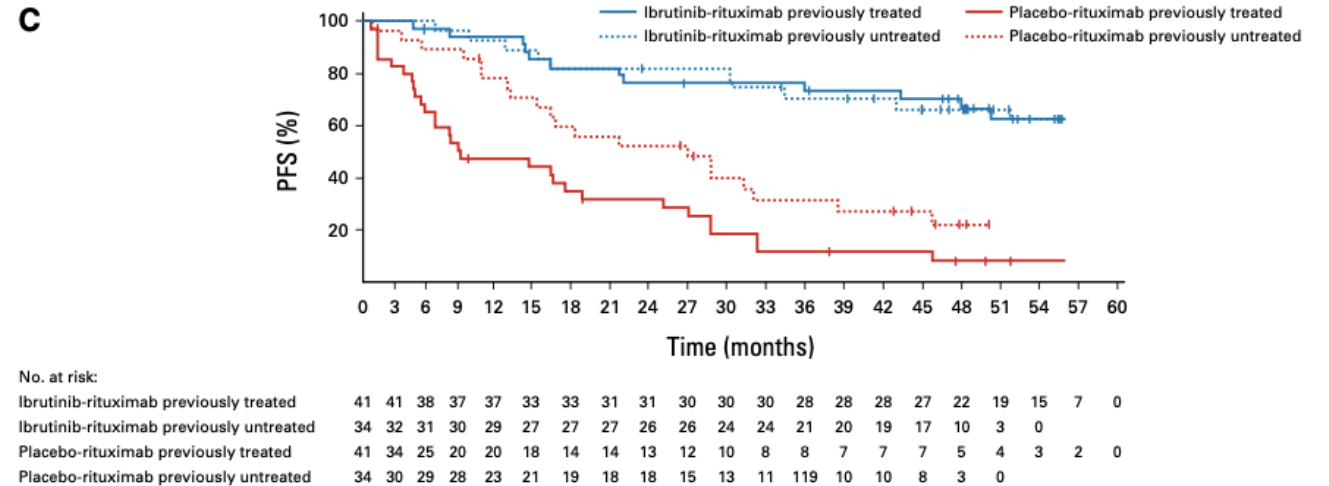
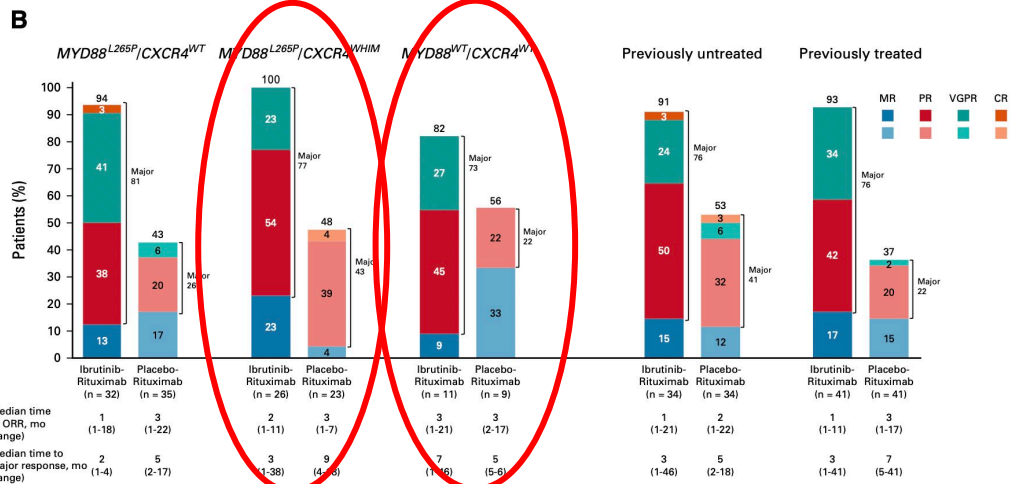
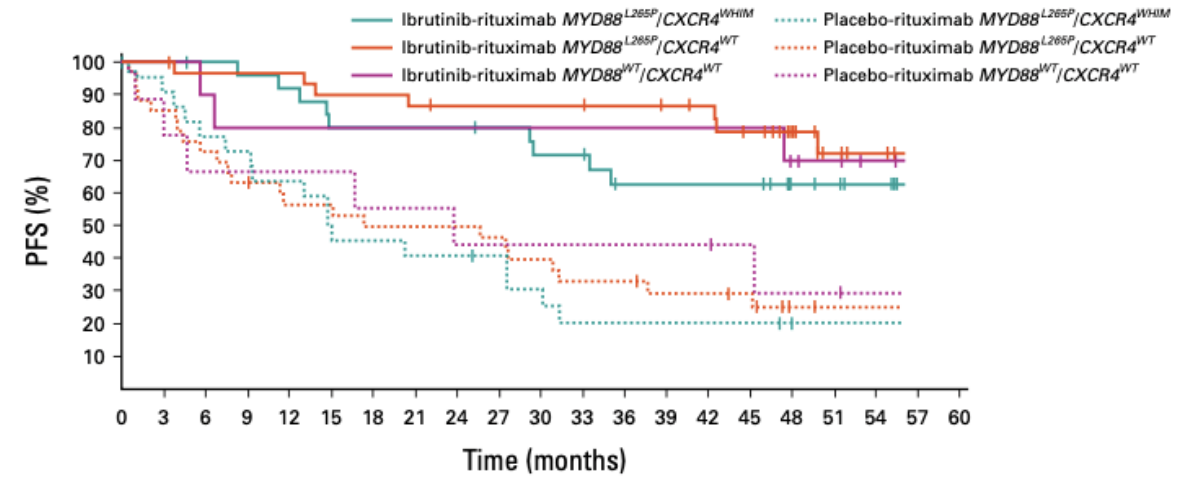
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|--|----|----|----|----|----|----|---|
| MYD88 ^{Mut} /CXCR4 ^{WT} | 36 | 35 | 29 | 29 | 22 | 18 | 0 |
| MYD88 ^{Mut} /CXCR4 ^{Mut} | 22 | 18 | 16 | 13 | 10 | 7 | 0 |
| MYD88 ^{WT} /CXCR4 ^{Mut} | 4 | 2 | 0 | 0 | 0 | 0 | 0 |

Ibrutinib plus Rituximab may overcome the impact of poor prognosis mutational patterns: the iNNOVATE trial



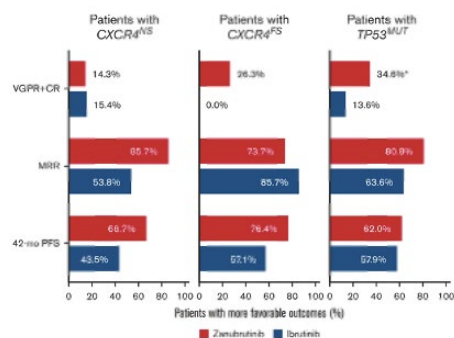
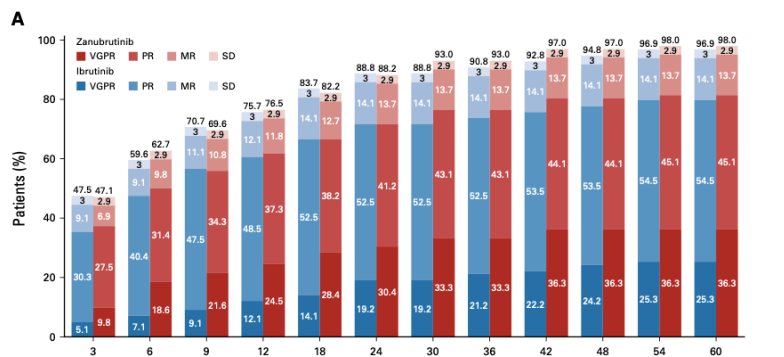
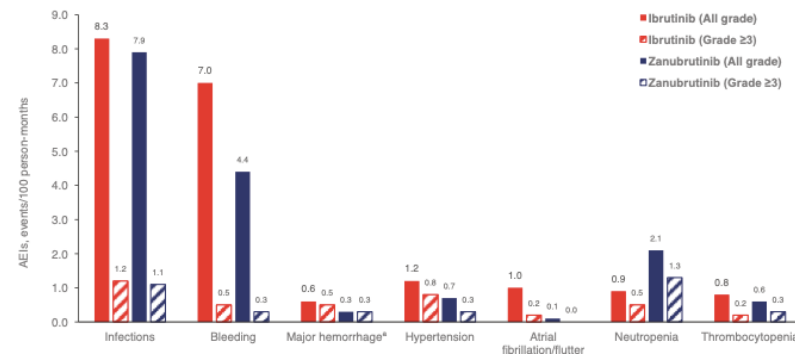
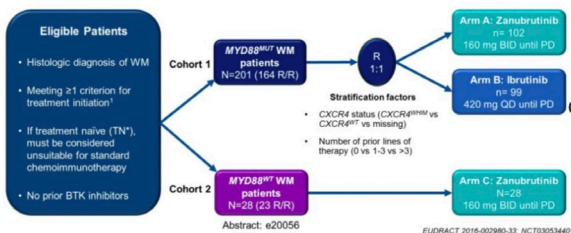
No. at risk:

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |
|---------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Ibrutinib-rituximab | 75 | 73 | 69 | 67 | 66 | 60 | 60 | 58 | 57 | 56 | 54 | 54 | 46 | 48 | 47 | 44 | 32 | 22 | 15 | 7 | |
| Placebo-rituximab | 75 | 64 | 54 | 48 | 43 | 39 | 33 | 32 | 31 | 27 | 23 | 19 | 19 | 17 | 17 | 15 | 7 | 4 | 3 | 2 | |

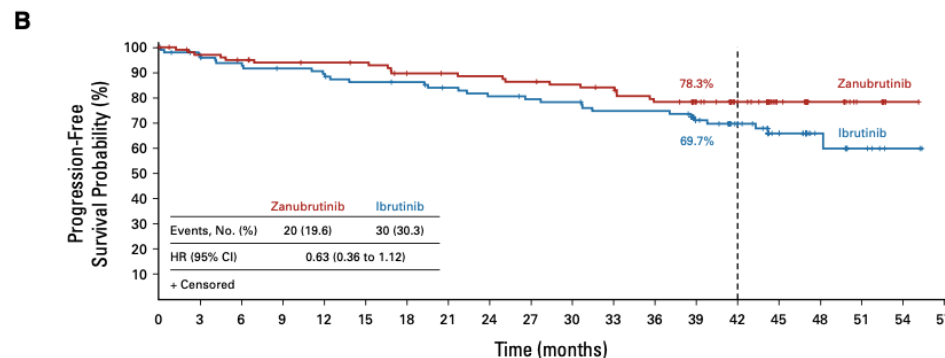


Next generation BTK inhibitors: Zanubrutinib compared to Ibrutinib

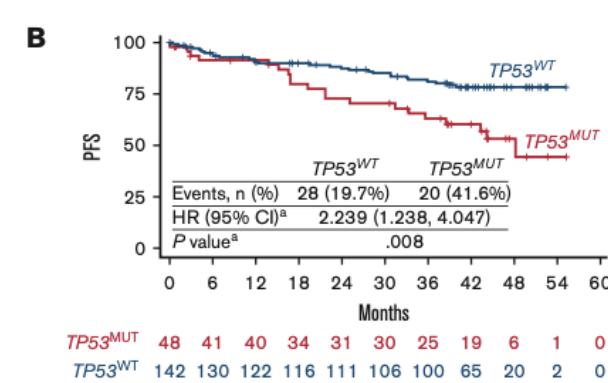
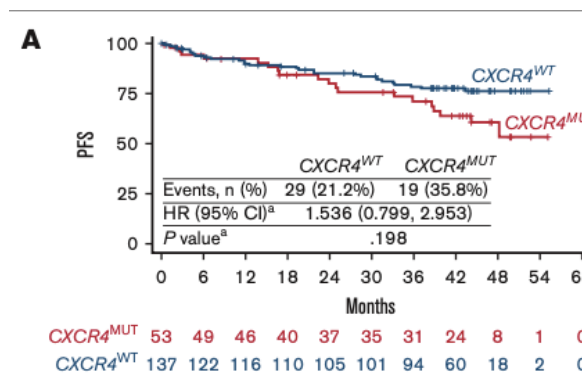
ASPEN trial



| | Zanubrutinib vs Ibrutinib | | |
|------------------------|-----------------------------------|------------------------------------|-----------------------------------|
| | Patients With CXCR4 ^{WT} | Patients With CXCR4 ^{MUT} | Patients With TP53 ^{MUT} |
| Median time to VGPR+CR | 10.3 mo vs 31.3 mo | 11.1 mo vs NE | 11.1 mo vs 24.9 mo |
| Median time to MRR | 4.1 mo vs 2.9 mo | 2.9 mo vs 7.0 mo | 2.8 mo vs 3.0 mo |
| Median PFS | NR vs 39.8 mo | NR vs 44.2 mo | NR vs 44.2 mo |

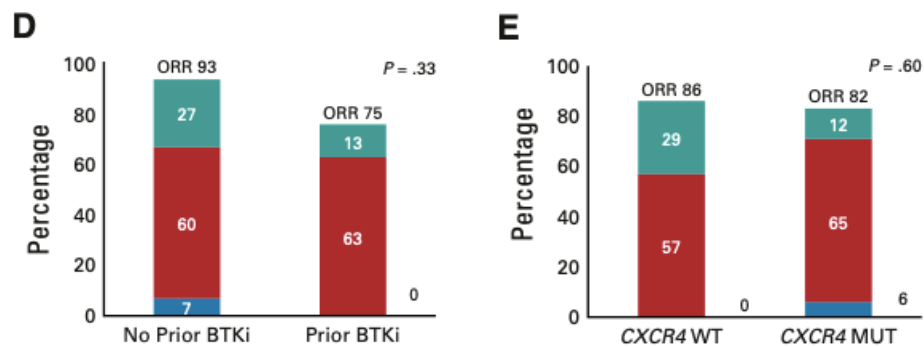
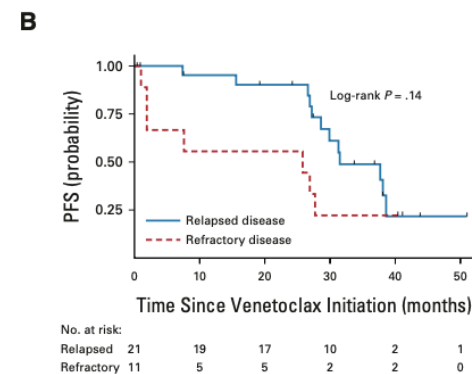
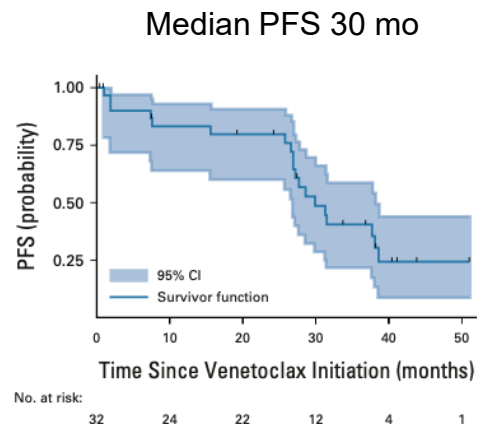
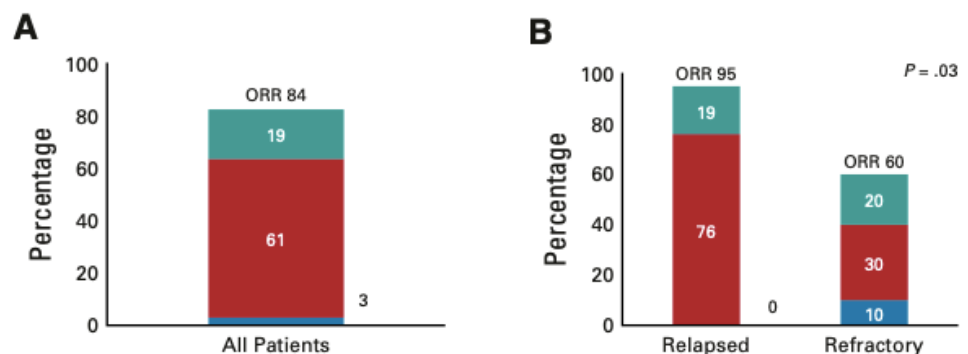


| No. of Patients at risk: | 102 | 96 | 93 | 90 | 89 | 88 | 82 | 81 | 80 | 78 | 76 | 74 | 68 | 60 | 43 | 25 | 15 | 8 | 1 | 0 |
|--------------------------|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|
| Zanubrutinib | 102 | 92 | 88 | 85 | 83 | 79 | 78 | 74 | 71 | 69 | 68 | 64 | 64 | 52 | 41 | 27 | 11 | 6 | 2 | 0 |
| Ibrutinib | 99 | 92 | 88 | 85 | 83 | 79 | 78 | 74 | 71 | 69 | 68 | 64 | 64 | 52 | 41 | 27 | 11 | 6 | 2 | 0 |

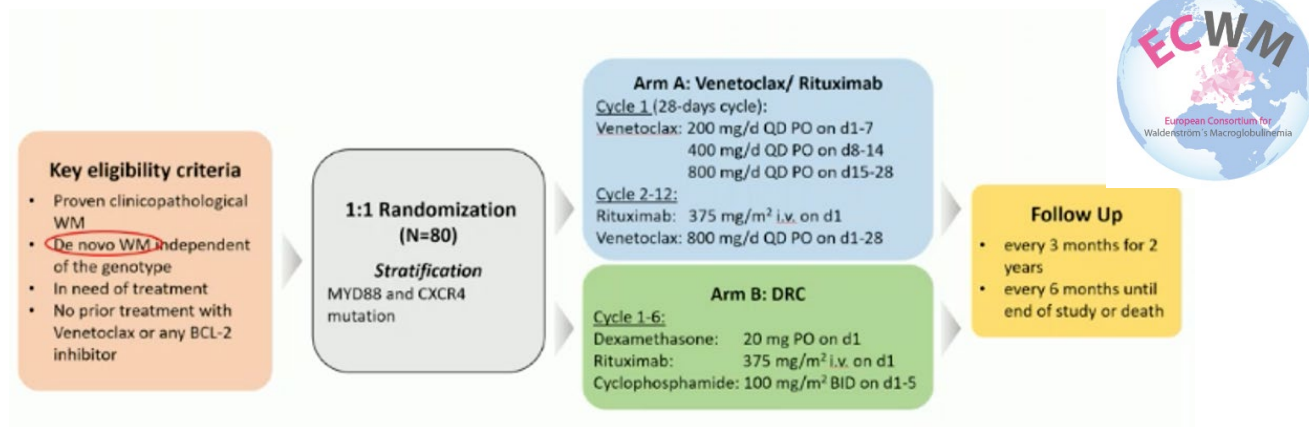


Novel agents: venetoclax for the treatment of relapsed refractory patients

32 pts in a phase 2 study with 33 mo median FU



MR PR VGPR



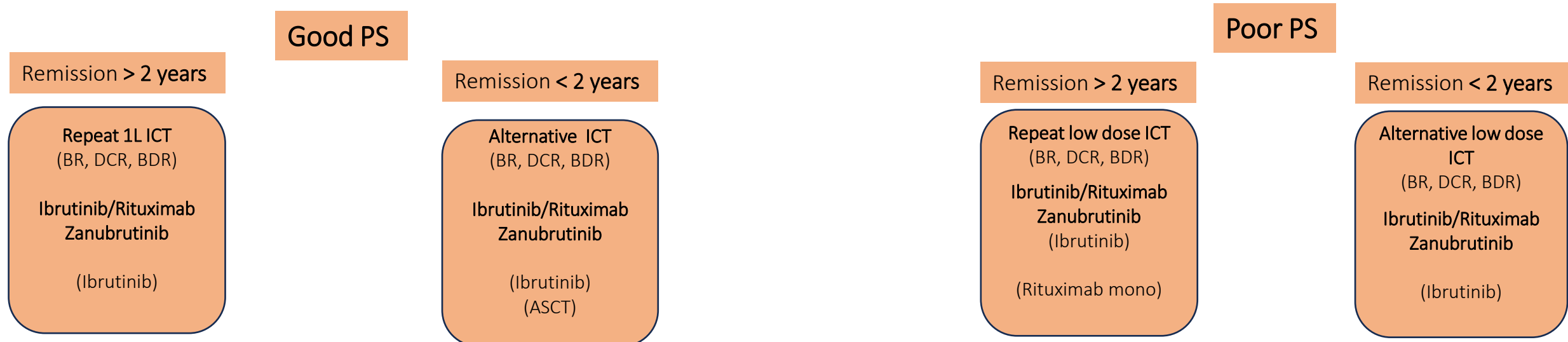
Primary objective: to determine the efficacy of time limited venetoclax plus Rituximab compared to classical DRC in newly diagnosed WM

Combinations using less toxic, non-covalent BTK inhibitor:
Pirtobrutinib plus Venetoclax for RR WM (NCT05734495)

In summary, 1L treatment approach (still based on ICT for most patients)

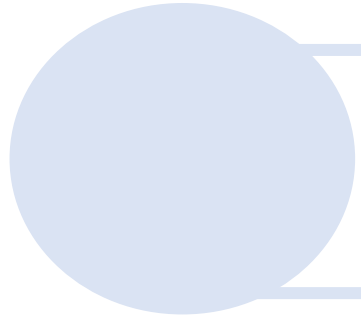


In summary, treatment approach for RR (depending on duration of 1st response)



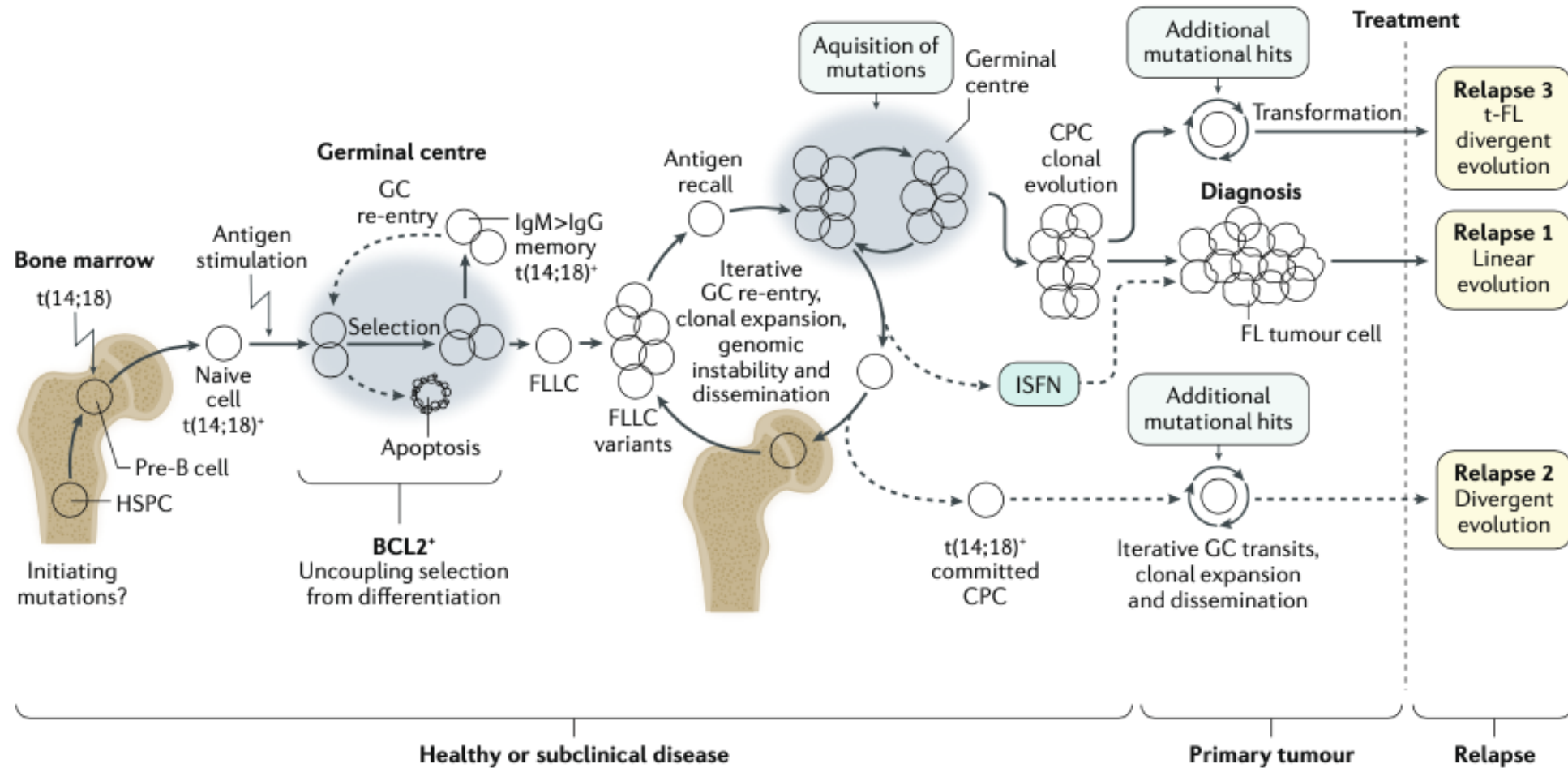
Take home messages

- Indolent lymphomas are frequent and prolonged survival is expected
- Clinical and biological heterogeneity exists between entities and within each entity
- For most entities, **first line** treatment options are defined (but can be challenged!)
- Large randomized **trials** are available for **FL** but mostly not for rarer diseases
- An increasing number of options are available, including **targeted agents and T cell engaging therapies**
- **Treatment sequencing** may be challenging and needs focused research



Back up slides

Pathogenesis and evolution of FL



ROSEWOOD: Zanubrutinib Obinutuzumab improve outcomes

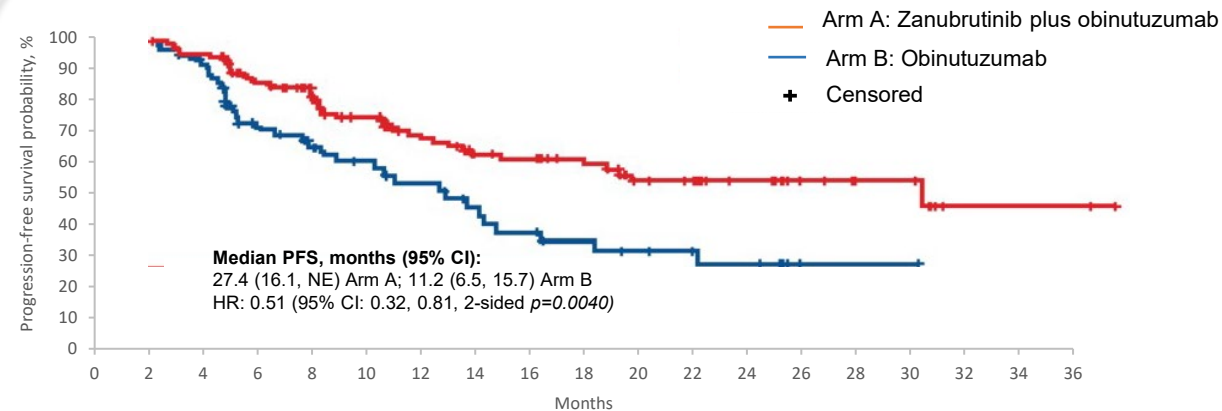
Disease Response by ICR

| | Zanubrutinib/ Obinutuzumab | Obinutuzumab | |
|------------------------------|-------------------------------|--------------|-----------------|
| ORR (95% CI) | 68.3% (60-75.7%) | 45.8% | p=0.0017 |
| Complete response | 37.2% | 19.4% | P=0.0083 |
| Partial response | 31% | 26.4% | |
| Stable disease | 17.2% | 19.4% | |
| Disease progression | 9% | 20.8% | |

29 patients crossed over to Zanubrutinib/obinutuzumab



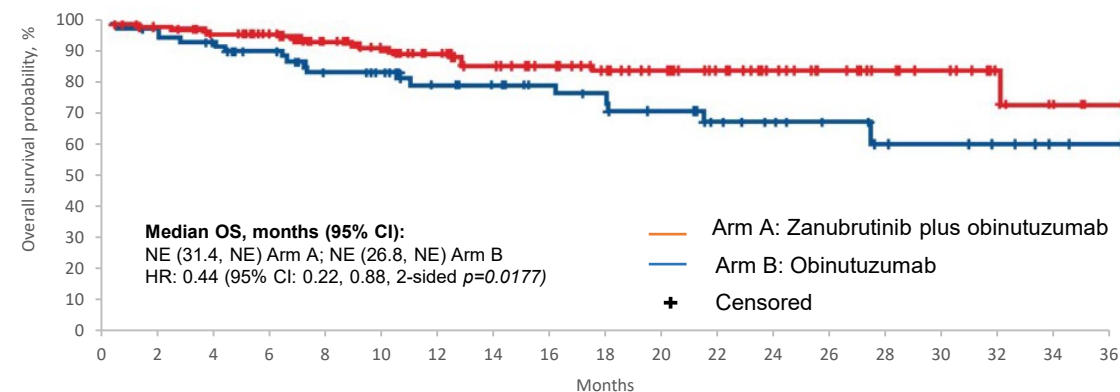
ORR: 24.1% (CR: 6.9%)



No. of patients at risk

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|---|
| 145 | 135 | 111 | 83 | 76 | 56 | 46 | 40 | 37 | 27 | 19 | 18 | 10 | 8 | 3 | 2 | 2 | 1 | 0 |
| 72 | 63 | 39 | 29 | 26 | 23 | 16 | 12 | 11 | 9 | 7 | 6 | 1 | 1 | 0 | | | | |

Median study follow-up 12.5 months

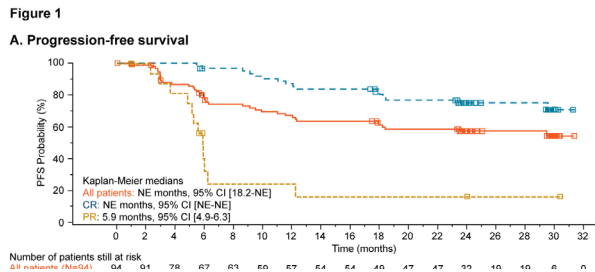
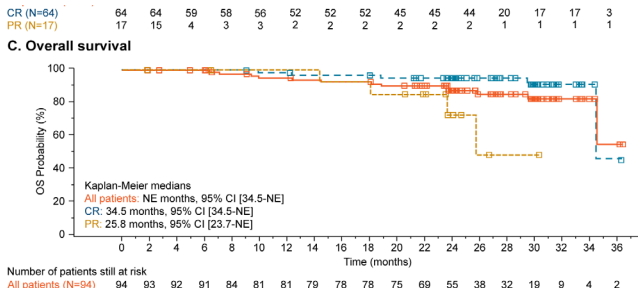


No. of patients at risk:

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|
| 145 | 139 | 132 | 121 | 104 | 89 | 75 | 64 | 58 | 51 | 42 | 36 | 28 | 22 | 15 | 12 | 5 | 3 | 0 |
| 72 | 67 | 63 | 57 | 50 | 45 | 39 | 32 | 29 | 25 | 23 | 17 | 12 | 11 | 7 | 7 | 4 | 1 | 0 |

ELARA – long term results with Tisa Cel

Median FU 29 mo



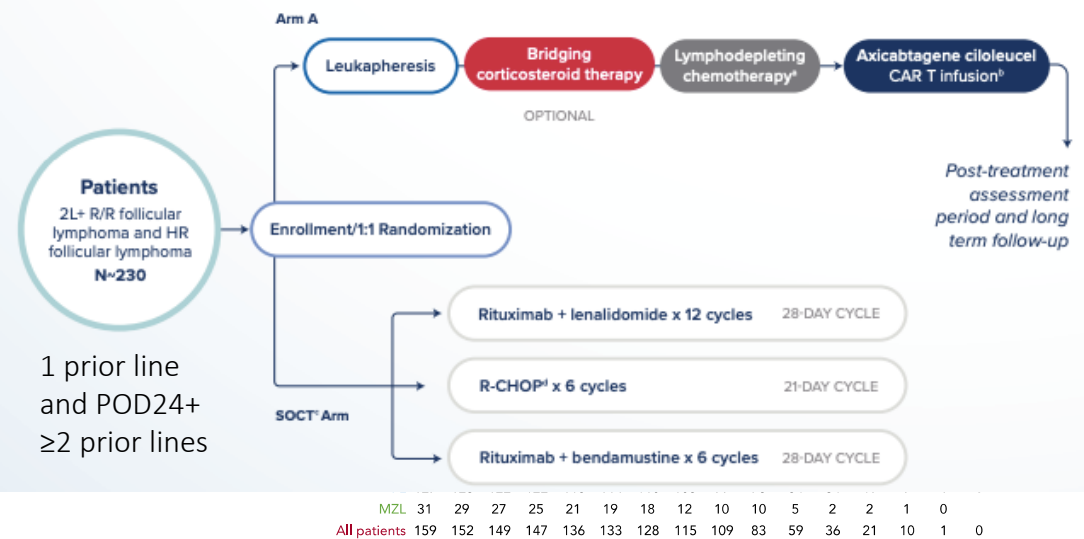
Dreyling M et al, Blood 2024 doi: 10.1182/blood.2023021567

ZUMA 5 – long term results with Axi Cel

Median FU 40 mo

ZUMA-22: A Phase 3 Randomized, Open-Label, Multicenter Study Evaluating the Efficacy of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Subjects With Relapsed/Refractory Follicular Lymphoma

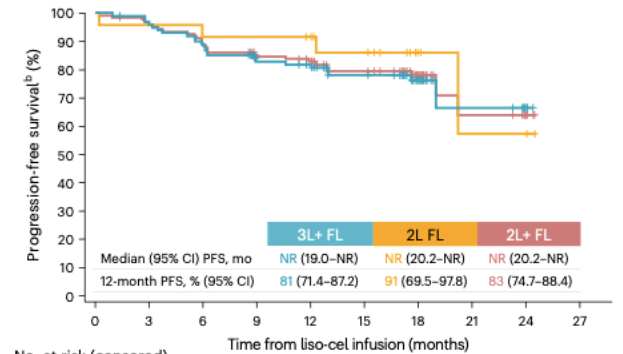
Study Design¹⁻³



Neelapu S et al, Blood 2024, 143 (6):496-506

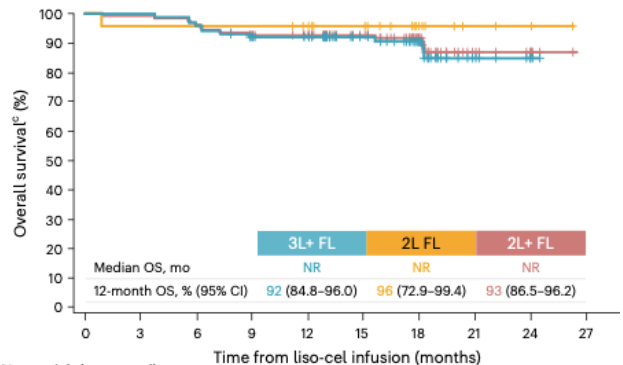
TRANSCEND FL – results with Liso Cel

Median FU 17.5- 17.8 mo



No. at risk (censored)

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 |
|--------|---------|---------|---------|--------|--------|---------|---------|--------|-------|-------|
| 3L+ FL | 101 (0) | 96 (1) | 89 (0) | 78 (6) | 72 (3) | 50 (20) | 19 (30) | 7 (11) | 2 (5) | 0 (2) |
| 2L FL | 23 (0) | 22 (0) | 21 (0) | 21 (0) | 20 (1) | 16 (3) | 5 (11) | 2 (2) | 2 (0) | 0 (2) |
| 2L+ FL | 124 (0) | 118 (1) | 110 (0) | 99 (6) | 92 (4) | 66 (23) | 24 (41) | 9 (13) | 4 (5) | 0 (4) |

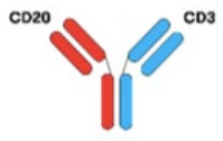
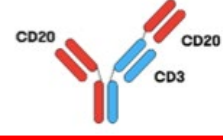

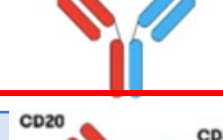
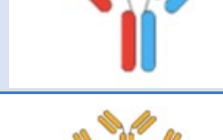
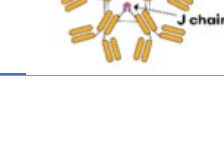


No. at risk (censored)

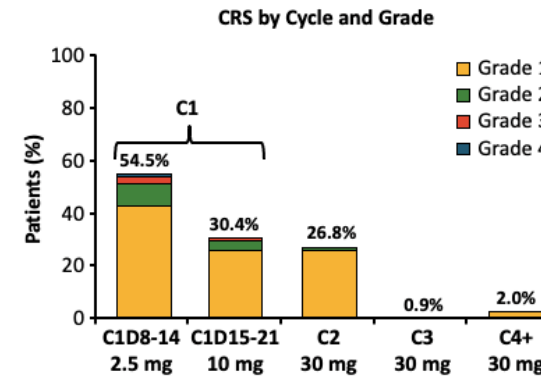
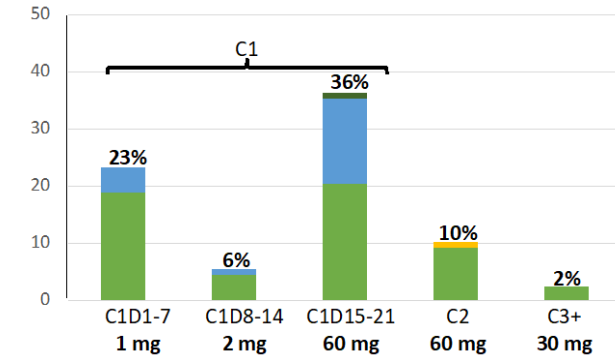
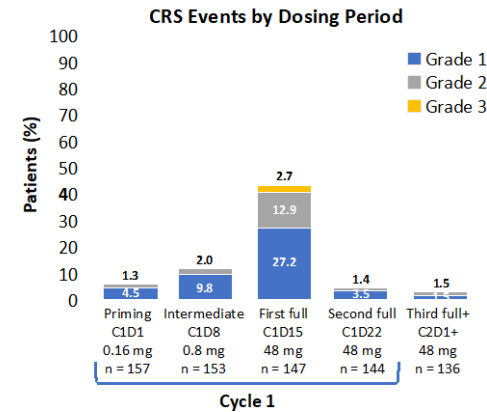
| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 |
|--------|---------|---------|---------|---------|---------|---------|---------|---------|-------|-------|
| 3L+ FL | 101 (0) | 101 (0) | 97 (0) | 90 (3) | 86 (4) | 63 (23) | 38 (24) | 11 (25) | 3 (8) | 0 (3) |
| 2L FL | 23 (0) | 22 (0) | 22 (0) | 22 (0) | 20 (2) | 17 (3) | 8 (9) | 3 (5) | 2 (1) | 0 (2) |
| 2L+ FL | 124 (0) | 123 (0) | 119 (0) | 112 (3) | 106 (6) | 80 (26) | 46 (33) | 14 (30) | 5 (9) | 0 (5) |

Morschhauser F et al, Nat Med 2024, 30: 2199-2207

CD3-CD20 bispecific antibodies for B cell lymphomas

| Antibody | Structure | Format | Administration |
|----------------------|---|--------|----------------|
| Mosunetuzumab |  | IgG1 | IV ou SC |
| Glofitamab |  | IgG1 | IV |
| Epcoritamab |  | IgG1 | SC |
| Odronextamab |  | IgG4 | IV or SC |
| Plamotamab |  | IgG1 | IV or SC |
| Invotamab |  | IgM | IV |

CRS



- Neurotoxicity
- Neutropenia
- Hipogamaglobulinemia
- Infections
- Tumor flare
- Tumor lysis

The future of bispecific antibodies: combinations and earlier use

Mosun (sc) + Lenalidomide 1L (phase 1b, n=40 pts)

Mosun sc (5>>45 mg) x 12 cycles (28d)

Maint 8/8w x 9

Lena 20mg/d x 21/28d x 12

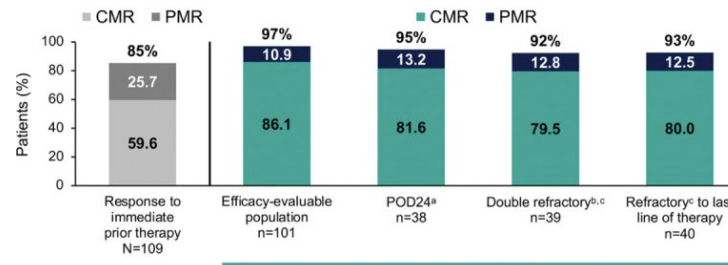
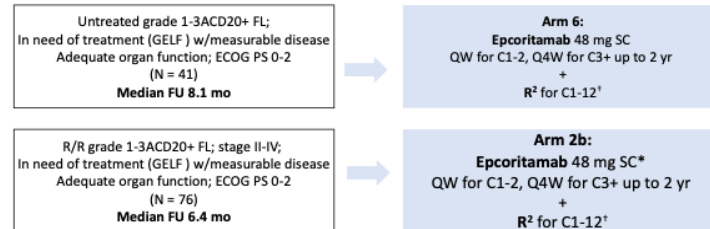
| | |
|--------------------|----------------|
| ORR CR (37 pts) | 91.9% 89.2% |
| CRS (all G 1-2) | 50% (cycle 1) |

NCT06284122:
Mosunetuzumab sc +
Lenalidomide
Compared to Anti-
CD20 Antibody +
Chemotherapy
in 1L Follicular
Lymphoma FLIPI 2-5
(MORNINGLYTE)

NCT04712097
Mosunetuzumab iv +
Lenalidomide
Compared to
Rituximab
Lenalidomide
in RR Follicular
Lymphoma in need of
treatment
(CELESTIMO)

Morschhauser F et al, *Blood* (2023) 142 (Supplement 1): 605.

EPCORE ph 1-2 NHL 2 (NCT04663347)



Sureda A, et al. *Hemasphere*. 2023;7 (Suppl):e5547136.

Belada, ICML 2023, abst 84

OLYMPIA 1 (NCT06091254) and 2 (NCT06097364)

Odronextamab for 6 cycles
followed by odronextamab maintenance

CIT* for 6 cycles
followed by rituximab maintenance

Odronextamab + CHOP/CVP for 6 cycles
no maintenance

Odronextamab + CHOP/CVP for 6 cycles
followed by odronextamab maintenance

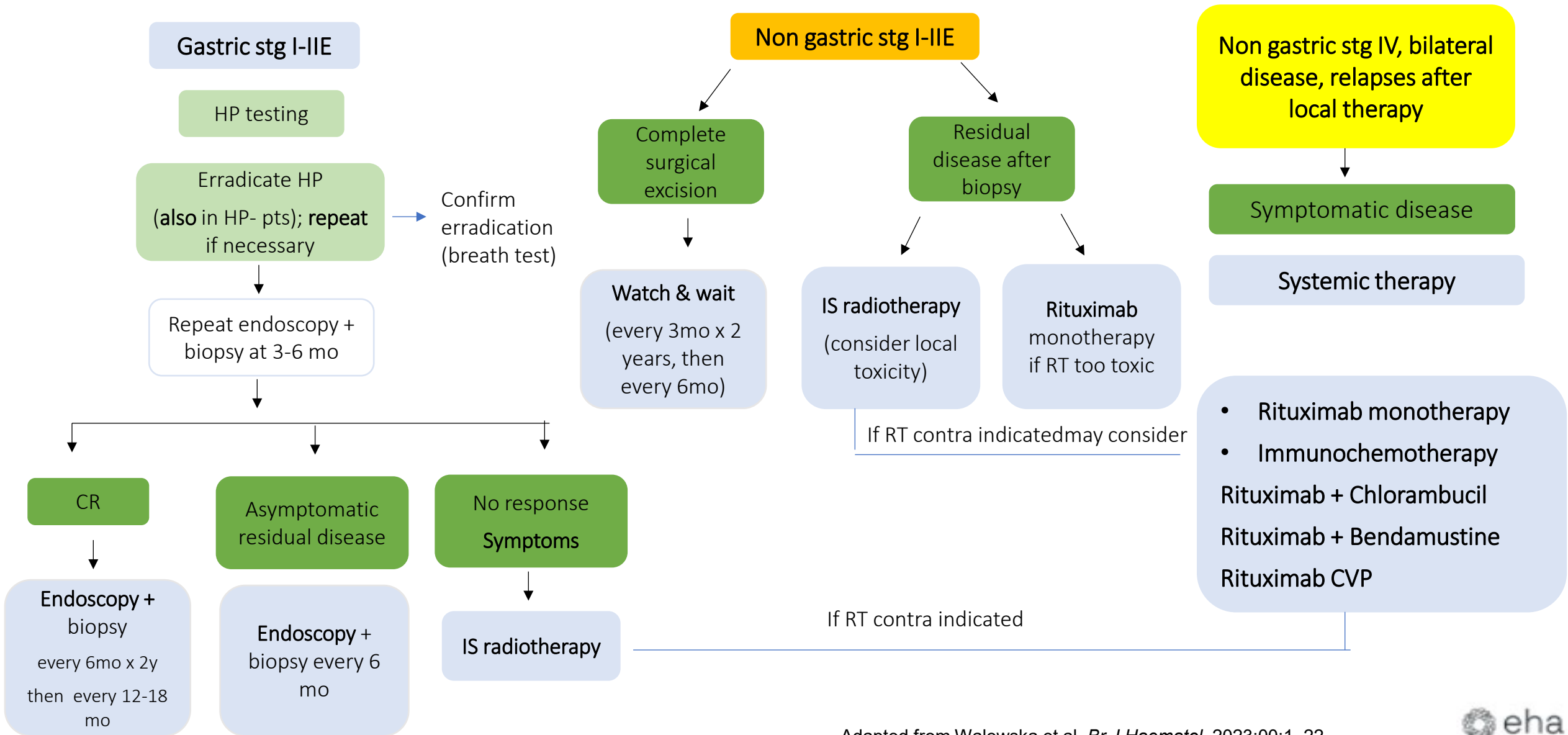
R-CHOP/R-CVP for 6 cycles
followed by rituximab maintenance

Luminari. *Hemasphere*. 2023;7(Suppl):e84791f4.
Novelli. *Hemasphere* 2023;7(Suppl):e384923b.

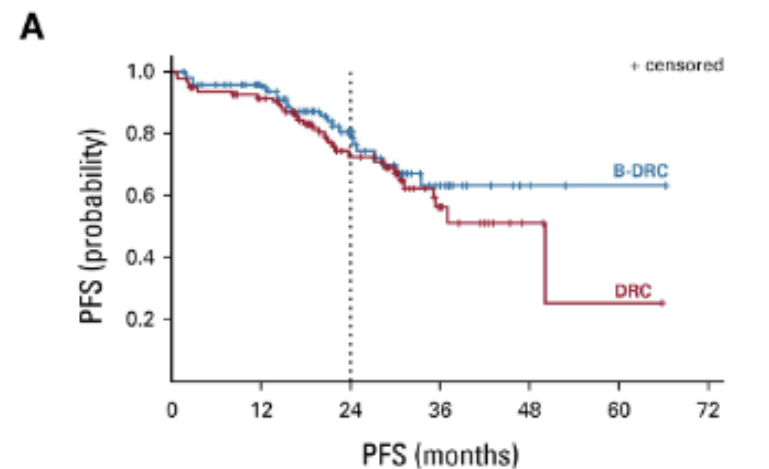
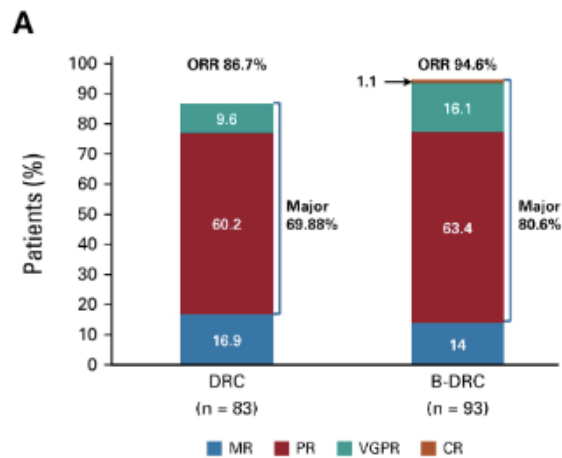
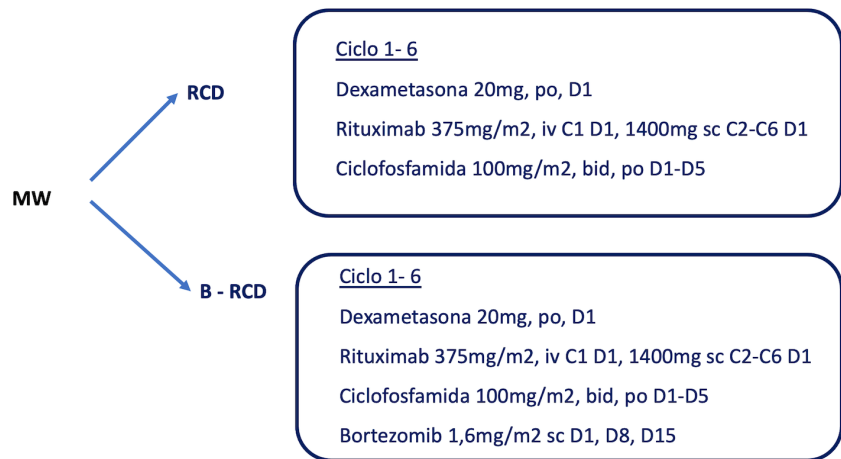
Staging of gastric MALT lymphoma

| Lugano staging system | | TNM (or Paris) staging system | Disease extension |
|-----------------------|---|-------------------------------|---|
| Stage I | I ₁ : confined to mucosa or submucosa | T1 N0 M0 | Mucosal or submucosal layer |
| | I ₂ : confined to muscularis propria or serosa | T2 N0 M0 | Muscularis propria |
| | | T3 N0 M0 | Serosa |
| Stage II | II ₁ : extending into abdomen with local nodal involvement | T1-3 N1 M0 | Perigastric lymph nodes |
| | II ₂ : extending into abdomen with distant nodal involvement | T1-3 N2 M0 | More distant regional lymph nodes |
| Stage IIE | Penetration of serosa to involve adjacent organs or tissues | T4 N0 M0 | Adjacent structures |
| Stage IV | Disseminated extranodal involvement or concomitant supradiaphragmatic involvement | T1-4 N3 M0 | Lymph nodes on both sides of the diaphragm |
| | | T1-4 N0-3 M1 | Bone marrow invasion, additional extranodal sites |

Therapeutic options for EMZL

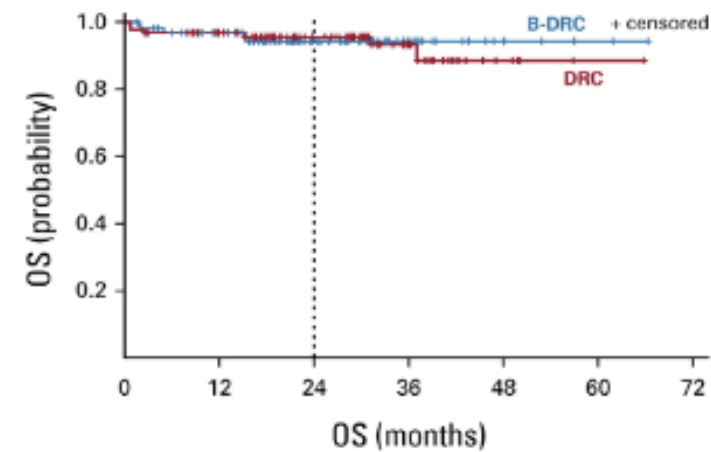


Is it worth to combine proteasome inhibitors with alkylating agents in WM?



No. at risk:

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|-------|-----|----|----|----|----|----|----|
| B-DRC | 102 | 83 | 42 | 14 | 3 | 1 | 0 |
| DRC | 100 | 81 | 44 | 17 | 3 | 1 | 0 |



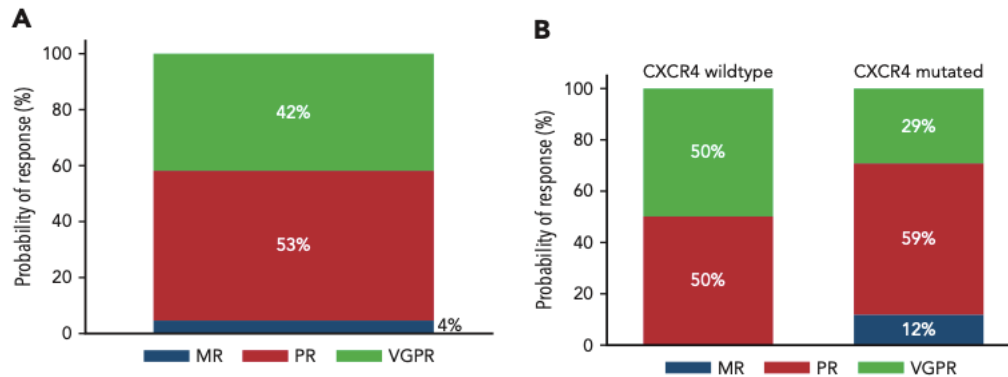
No. at risk:

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|-------|-----|----|----|----|----|----|----|
| B-DRC | 102 | 84 | 47 | 19 | 5 | 2 | 0 |
| DRC | 100 | 84 | 56 | 26 | 5 | 1 | 0 |

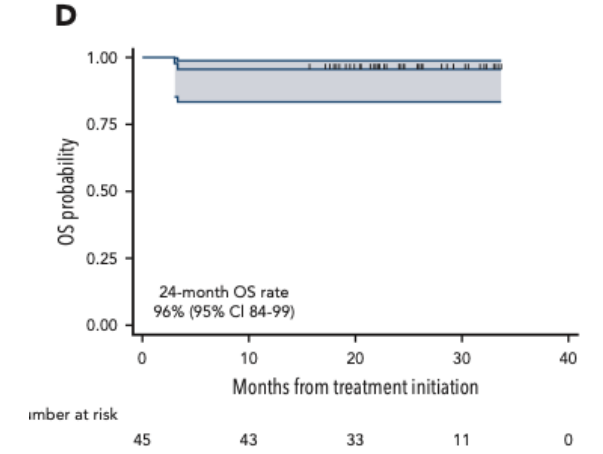
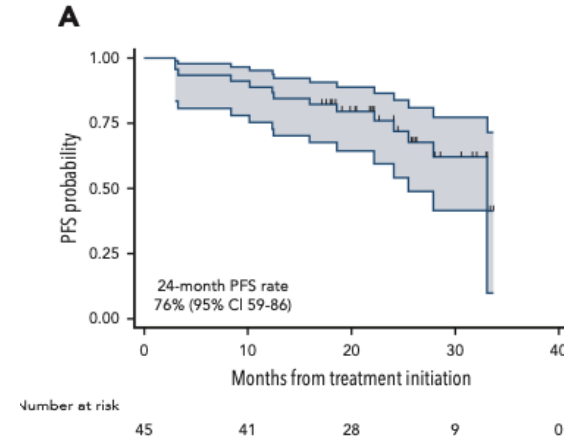
Fixed duration combinations including BTK inhibitors

Ibrutinib and venetoclax as primary therapy in symptomatic, treatment-naïve Waldenström macroglobulinemia

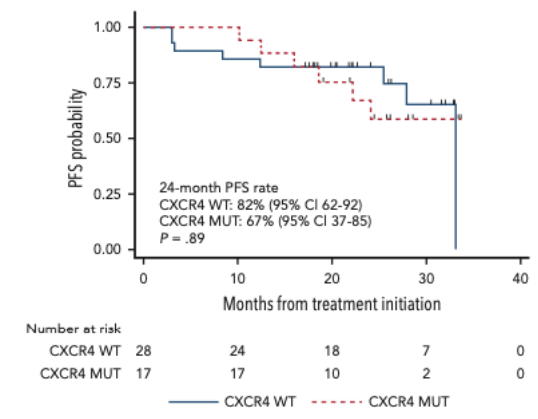
Castillo J et al, Blood 2024, 143: 582



N=45 TN pts, median 67yo
 17/45 pts with CXCR4 mut
 Planned 24 cycles (median time on treatment 10,2 mo)
 VGPR 42%



- Grade ≥3 AE:
 38% neutropenia
 9% mucosites
 7% TLS
- AF 9%
- Ventricular arrhythmias
 9% (2 fatal)



➔ Combinations using less toxic agents:
 Pirtobrutinib plus Venetoclax for RR WM (NCT05734495)